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(54) **NUCLEIC ACID AND AMINO ACID SEQUENCES FOR ATP-BINDING CASSETTE TRANSPORTER AND METHODS OF SCREENING FOR AGENTS THAT MODIFY ATP-BINDING CASSETTE TRANSPORTER**

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This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

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(51) **Int. Cl.**

C12N 5/00 (2006.01)
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C07H 21/02 (2006.01)
C07H 21/04 (2006.01)
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(52) **U.S. Cl.** **435/325**; 435/69.1; 435/320.1; 435/455; 536/23.1; 536/23.5; 530/350

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides nucleic acid and amino acid sequences of an ATP binding cassette transporter and mutated sequences thereof associated with macular degeneration. Methods of detecting agents that modify ATP-binding cassette transporter comprising combining purified ATP binding cassette transporter and at least one agent suspected of modifying the ATP binding cassette transporter and observing a change in at least one characteristic associated with ATP binding cassette transporter. Methods of detecting macular degeneration is also embodied by the present invention.

5 Claims, 19 Drawing Sheets

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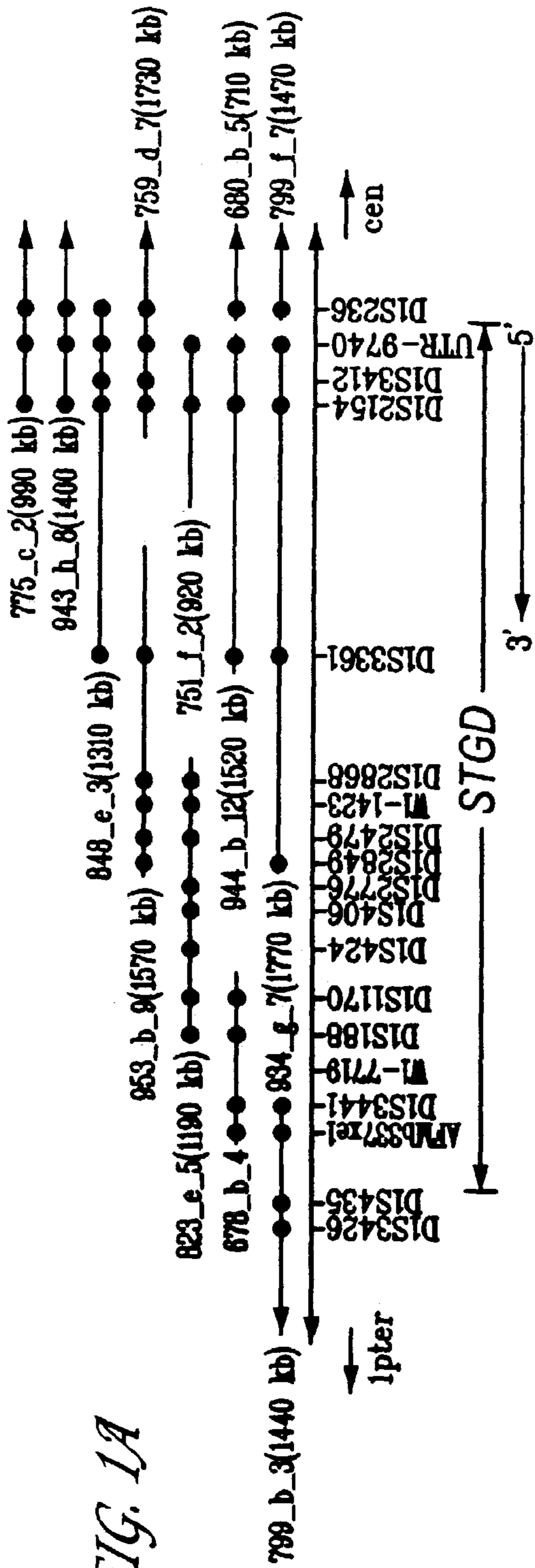


FIG. 1A

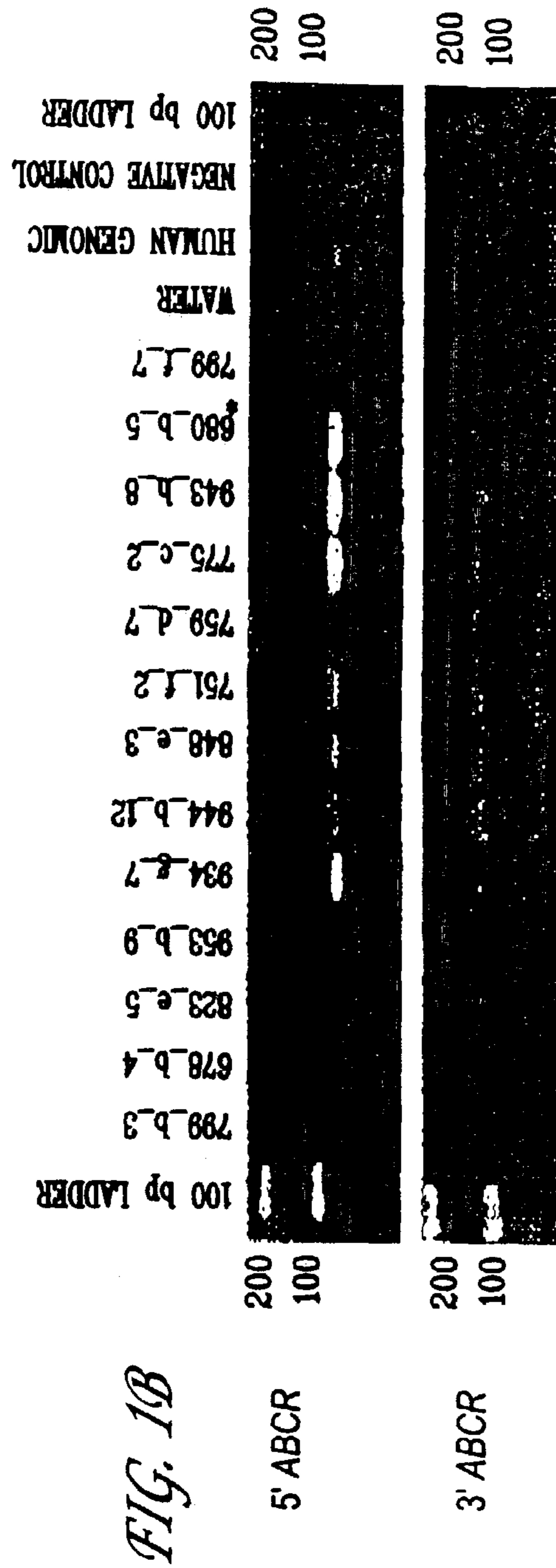


FIG. 1B

B H K Li Lu R S

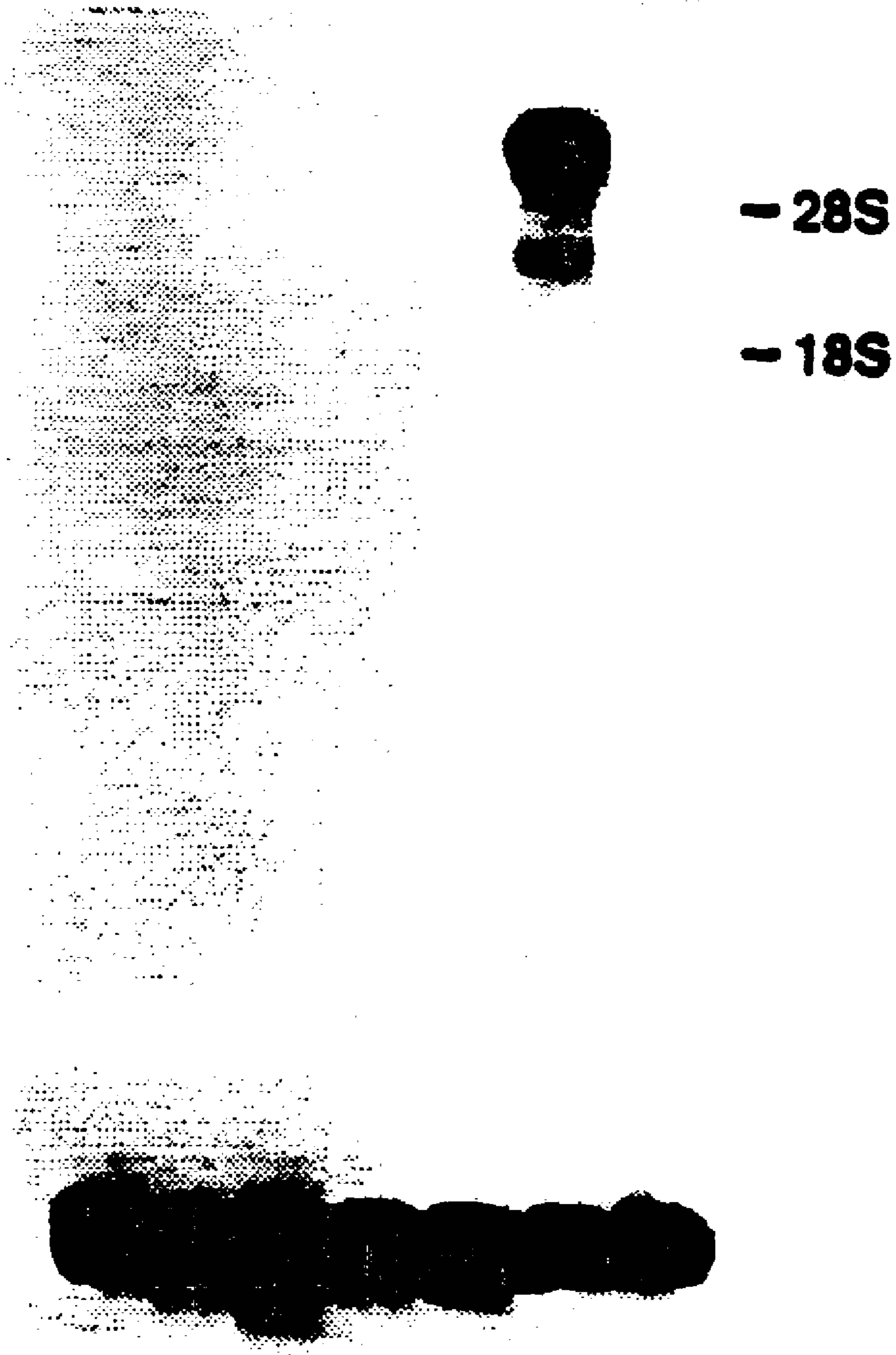


FIG. 2

-580 -560 -540
 CCCCTACCCCTCTGCTAAGCTCAGGGATAACCCAACCTAGCTGACCATAATGACTTCAGTC
 -520 -500 -480
 ATTACGGAGCAAGATGAAAGACTAAAAGAGGGAGGGATCACTTCAGATCTGCCGAGTGAG
 -460 -440 -420
 TCGATTGGACTTAAAGGGCCAGTCAAACCCTGACTGCCGGCTCATGGCAGGCTCTTGCCG
 -400 -380 -360
 AGGACAAATGCCCAGCCTATATTTATGCAAAGAGATTTTGTTCCAAACCTTAAGGTCAAAG
 -340 -320 -300
 ATACCTAAAGACATCCCCCTCAGGAACCCCTCTCATGGAGGAGAGTGCCTGAGGGTCTTG
 -280 -260 -240
 GTTCCCATTGCATCCCCACCTCAATTTCCCTGGTGCCAGCCACTTGTGTCTTTAGGG
 -220 -200 -180
 TTCTCTTCTCTCCATAAAAGGGAGCCAACACAGTGTCCGCCTCCTCTCCCCAACTAAGG
 -160 -140 -120
 GCTTATGTGTAATTAAGGGATTATGCTTTGAAGGGGAAAAGTAGCCTTTAATCACCAG
 -100 -80 -60
 GAGAAGGACACAGCGTCCGGAGCCAGAGGCGCTCTTAACGGCGTTTATGTCCTTTGCTGT
 -40 -20 0
 CCTGAGGGGCCTCAGCTCTGACCAATCTGGTCTTCGTGTGGTCATTAGCATGGGCTTCGT
 M G F V
 20 40 60
 GAGACAGATACAGCTTTTGCTCTGGAAGAACTGGACCCTGCGGAAAAGGCCAAAAGATTTCG
 R Q I Q L L L W K N W T L R K R Q K I R
 80 100 120
 CTTTGTGGTGGAACCTCGTGTGGCCTTTATCTTTATTTCTGGTCTTGATCTGGTTAAGGAA
 F V V E L V W P L S L F L V L I W L R N
 140 160 180
 TGCCAACCCGCTCTACAGCCATCATGAAT|GCCATTTCCCAACAAGGCGATGCCCTCAGC
 A N P L Y S H H E C H F P N K A M P S A
 200 220 240
 AGGAATGCTGCCGTGGCTCCAGGGGATCTTCTGCAATGTGAACAATCCCTGTTTTCAAAG
 G M L P W L Q G I F C N V N N P C F Q S
 260 280 300
 CCCACCCAGGAGAATCTCCTGGAATTGTGTCAAACCTATAACAACCTCCAT|CTTGGCAAG
 P T P G E S P G I V S N Y N N S I L A R
 320 340 360
 GGTATATCGAGATTTTCAAGAACTCCTCATGAATGCACCAGAGAGCCAGCACCTTGGCCG
 V Y R D F Q E L L M N A P E S Q H L G R
 380 400 420
 TATTTGGACAGAGCTACACATCTTGTCCCAATTCATGGACACCCTCCGGACTCACCCGGA
 I W T E L H I L S Q F M D T L R T H P E
 440 460 480
 GAGAATTGCAG|GAAGAGGAATACGAATAAGGGATATCTTGAAAGATGAAGAAACACTGAC
 R I A G R G I R I R D I L K D E E T L T
 500 520 540
 ACTATTTCTCATTAAAACATCGGCCTGTCTGACTCAGTGGTCTACCTTCTGATCAACTC
 L F L I K N I G L S D S V V Y L L I N S

FIG. 3A

560 580 600
 TCAAGTCCGTCCAGAGCAG|TTCGCTCATGGAGTCCCGGACCTGGCGCTGAAGGACATCGC
 Q V R P E Q F A H G V P D L A L K D I A
 620 640 660
 CTGCAGCGAGGCCCTCCTGGAGCGCTTCATCATCTTCAGCCAGAGACGCGGGGCAAAGAC
 C S E A L L E R F I I F S Q R R G A K T
 680 700 720
 GGTGCGCTATGCCCTGTGCTCCCTCTCCCAGGGCACCCCTACAGTGGATAGAAGACACTCT
 V R Y A L C S L S Q G T L Q W I E D T L
 740 760 780
 GTATGCCAACGTGGACTTCTTCAAGCTCTTCCGTGTG|CTTCCCACACTCCTAGACAGCCG
 Y A N V D F F K L F R V L P T L L D S R
 800 820 840
 TTCTCAAGGTATCAATCTGAGATCTTGGGGAGGAATATTATCTGATATGTCACCAAGAAT
 S Q G I N L R S W G G I L S D M S P R I
 860 880 900
 TCAAGAG|TTTATCCATCGGCCGAGTATGCAGGACTTGCTGTGGGTGACCAGGCCCTCAT
 Q E F I H R P S M Q D L L W V T R P L M
 920 940 960
 GCAGAATGGTGGTCCAGAGACCTTTACAAAGCTGATGGGCATCCTGTCTGACCTCCTGTG
 Q N G G P E T F T K L M G I L S D L L C
 980 1000 1020
 TGGCTACCCCGAGGGAGGTGGCTCTCGGGTGTCTCCTTCAACTGGTATGAAGACAATAA
 G Y P E G G G S R V L S F N W Y E D N N
 1040 1060 1080
 CTATAAGGCCTTTCTGGGGATTGACTCCACAAGGAAGGATCCTATCTATTCTTATGACAG
 Y K A F L G I D S T R K D P I Y S Y D R
 1100 1120 1140
 AAGAACAA|CATCCTTTTGTAATGCATTGATCCAGAGCCTGGAGTCAAATCCTTTAACCAA
 R T T S F C N A L I Q S L E S N P L T K
 1160 1180 1200
 AATCGCTTGGAGGGCGGCAAAGCCTTTGCTGATGGGAAAATCCTGTACACTCCTGATTC
 I A W R A A K P L L M G K I L Y T P D S
 1220 1240 1260
 ACCTGCAGCACGAAGGATACTGAAGAAT|GCCAACTCAACTTTTGAAGAACTGGAACACGT
 P A A R R I L K N A N S T F E E L E H V
 1280 1300 1320
 TAGGAAGTTGGTCAAAGCCTGGGAAGAAGTAGGGCCCCAGATCTGGTACTTCTTTGACAA
 R K L V K A W E E V G P Q I W Y F F D N
 1340 1360 1380
 CAGCACACAGATGAACATGATCAGA|GATACCCTGGGGAACCCAACAGTAAAAGACTTTTT
 S T Q M N M I R D T L G N P T V K D F L
 1400 1420 1440
 GAATAGGCAGCTTGGTGAAGAAGGTATTACTGCTGAAGCCATCCTAAACTTCCTCTACAA
 N R Q L G E E G I T A E A I L N F L Y K
 1460 1480 1500
 GGGCCCTCGGGAAAGCCAGGCTGACGACATGGCCAACCTCGACTGGAGGGACATATTTAA
 G P R E S Q A D D M A N F D W R D I F N
 1520 1540 1560
 CATCACTGATCGCACCCCTCCGCCTGGTCAATCAATACCTGGAG|TGCTTGGTCCTGGATAA
 I T D R T L R L V N Q Y L E C L V L D K

FIG. 3B

1580 1600 1620
 GTTTGAAAGCTACAATGATGAAACTCAGCTCACCCAACGTGCCCTCTCTCTACTGGAGGA
 F E S Y N D E T Q L T Q R A L S L L E E
 1640 1660 1680
 AAACATGTTCTGGGCCGGAGTGGTATTCCTGACATGTATCCCTGGACCAGCTCTCTACC
 N M F W A G V V F P D M Y P W T S S L P
 1700 1720 1740
 ACCCCACGTGAAGTATAAGATCCGAATGGACATAGACGTGGTGGAGAAAACCAATAAGAT
 P H V K Y K I R M D I D V V E K T N K I
 1760 1780 1800
 TAAAGACAG|GTATTGGGATTCTGGTCCCAGAGCTGATCCCGTGGAAGATTTCCGGTACAT
 K D R Y W D S G P R A D P V E D F R Y I
 1820 1840 1860
 CTGGGGCGGGTTTGCCTATCTGCAGGACATGGTTGAACAGGGGATCACAAGGAGCCAGGT
 W G G F A Y L Q D M V E Q G I T R S Q V
 1880 1900 1920
 GCAGGCGGAGGCTCCAGTTGGAATCTACCTCCAGCAGATGCCCTACCCCTGCTTCGTGGA
 Q A E A P V G I Y L Q Q M P Y P C F V D
 1940 1960 1980
 CGATTC|TTTCATGATCATCCTGAACCGCTGTTCCCTATCTTCATGGTGTGGCATGGAT
 D S F M I I L N R C F P I F M V L A W I
 2000 2020 2040
 CTACTCTGTCTCCATGACTGTGAAGAGCATCGTCTTGGAGAAGGAGTTGCCACTGAAGGA
 Y S V S M T V K S I V L E K E L R L K E
 2060 2080 2100
 GACCTTGAAAATCAGGGTGTCTCCAATGCAGTGATTTGGTGTACCTGGTTCCTGGACAG
 T L K N Q G V S N A V I W C T W F L D S
 2120 2140 2160
 CTTCTCCATCATGTCGATGAGCATCTTCCTCCTGACGATATTCATCATGCATG|GAAGAAT
 F S I M S M S I F L L T I F I M H G R I
 2180 2200 2220
 CCTACACTACAGCGACCCATTCATCCTCTTCCTGTTCTTGTGGCTTTCTCCACTGCCAC
 L H Y S D P F I L F L F L L A F S T A T
 2240 2260 2280
 CATCATGCTGTGCTTTCTGCTCAGCACCTTCTTCTCCAAGGCCAGTCTGGCAGCAGCCTG
 I M L C F L L S T F F S K A S L A A A C
 2300 2320 2340
 TAGTGGTGTGTCATCTATTTACCCTCTACCTGCCACACATCCTGTGCTTCGCCTGGCAGGA
 S G V I Y F T L Y L P H I L C F A W Q D
 2360 2380 2400
 CCGCATGACCGCTGAGCTGAAGAAGGCTGTG|AGCTTACTGTCTCCGGTGGCATTGATT
 R M T A E L K K A V S L L S P V A F G F
 2420 2440 2460
 TGGCACTGAGTACCTGGTTCGCTTTGAAGAGCAAGGCCTGGGGCTGCAGTGGAGCAACAT
 G T E Y L V R F E E Q G L G L Q W S N I
 2480 2500 2520
 CGGGAACAGTCCCACGGAAGGGGACGAATTCAGCTTCCTGCTGTCCATGCAGATGATGCT
 G N S P T E G D E F S F L L S M Q M M L
 2540 2560 2580
 CCTTGATGCTGCGTGCTATGGCTTACTCGCTTGGTACCTTGATCAGGTGTTTCCAG|GAGA
 L D A A C Y G L L A W Y L D Q V F P G D

FIG. 3C

2600 2620 2640
CTATGGAACCCCACTTCCTTGGTACTTTCTTCTACAAGAGTCGTATTGGCTTAGCGGTGA
Y G T P L P W Y F L L Q E S Y W L S G E
2660 2680 2700
AG|GGTGTTC AACCAGAGAAGAAAGAGCCCTGGAAAAGACCGAGCCCCTAACAGAGGAAAC
G C S T R E E R A L E K T E P L T E E T
2720 2740 2760
GGAGGATCCAGAGCACCCAGAAGGAATACACG|ACTCCTTCTTTGAACGTGAGCATCCAGG
E D P E H P E G I H D S F F E R E H P G
2780 2800 2820
GTGGGTTCTGGGGTATGCGTGAAGAATCTGGTAAAGATTTTTGAGCCCTGTGGCCGGCC
W V P G V C V K N L V K I F E P C G R P
2840 2860 2880
AGCTGTGGACCGTCTGAACATCACCTTCTACGAGAACCAGATCACCGCATTCCTGGGCCA
A V D R L N I T F Y E N Q I T A F L G H
2900 2920 2940
CAATGGAGCTGGGAAAACCACCACCTT|GTCCATCCTGACGGGTCTGTTGCCACCAACCTC
N G A G K T T T L S I L T G L L P P T S
2960 2980 3000
TGGGACTGTGCTCGTTGGGGGAAGGGACATTGAAACCAGCCTGGATGCAGTCCGGCAGAG
G T V L V G G R D I E T S L D A V R Q S
3020 3040 3060
CCTTGGCATGTGTCCACAGCACAACATCCTGTTCCACCA|CCTCACGGTGGCTGAGCACAT
L G M C P Q H N I L F H H L T V A E H M
3080 3100 3120
GCTGTTCTATGCCAGCTGAAAGGAAAGTCCCAGGAGGAGGCCAGCTGGAGATGGAAGC
L F Y A Q L K G K S Q E E A Q L E M E A
3140 3160 3180
CATGTTGGAGGACACAGGCCTCCACCACAAGCGGAATGAAGAGGCTCAGGACCTATCAG|G
M L E D T G L H H K R N E E A Q D L S G
3200 3220 3240
TGGCATGCAGAGAAAGCTGTCGGTTGCCATTGCCCTTTGTGGGAGATGCCAAGGTGGTGAT
G M Q R K L S V A I A F V G D A K V V I
3260 3280 3300
TCTGGACGAACCCACCTCTGGGGTGGACCCTTACTCGAGACGCTCAATCTGGGATCTGCT
L D E P T S G V D P Y S R R S I W D L L
3320 3340 3360
CCTGAAGTATCGCTCAG|GCAGAACCATCATCATGCCCACTCACCACATGGACGAGGCCGA
L K Y R S G R T I I M P T H H M D E A D
3380 3400 3420
CCACCAAGGGGACCGCATTGCCATCATTGCCAGGGAAGGCTCTACTGCTCAGGCACCCC
H Q G D R I A I I A Q G R L Y C S G T P
3440 3460 3480
ACTCTTCTGAAGAACTGCTTTGGCACAGGCTTGTACTTAACCTTGGTGCGCAAGATGAA
L F L K N C F G T G L Y L T L V R K M K
3500 3520 3540
AAACATCCAGAGCCAAAGGAAAGGCAGTGAG|GGGACCTGCAGCTGCTCGTCTAAGGGTTT
N I Q S Q R K G S E G T C S C S S K G F
3560 3580 3600
CTCCACCACGTGTCCAGCCCACGTGCATGACCTAACTCCAGAACAAGTCCTGGATGGGGA
S T T C P A H V D D L T P E Q V L D G D

FIG. 3D

3620 3640 3660
 TGTAATGAGCTGATGGATGTAGTTCTCCACCATGTTCCAGAGGCAAAGCTGGTGGAGTG
 V N E L M D V V L H H V P E A K L V E C
 3680 3700 3720
 CATTGGTCAAGAACTTATCTTCCTTCTTCCAAATAAGAACTTCAAGCACAGAGCATATGC
 I G Q E L I F L L P N K N F K H R A Y A
 3740 3760 3780
 CAGCCTTTTCAGAGAGCTGGAGGAGACGCTGGCTGACCTTGGTCTCAGCAGTTTTTGAAT
 S L F R E L E E T L A D L G L S S F G I
 3800 3820 3840
 TTCTGACACTCCCCTGGAAGAG|ATTTTTCTGAAGGTCACGGAGGATTCTGATTCAGGACC
 S D T P L E E I F L K V T E D S D S G P
 3860 3880 3900
 TCTGTTTGCGG|GTGGCGCTCAGCAGAAAAGAGAAAACGTCAACCCCGACACCCCTGCTT
 L F A G G A Q Q K R E N V N P R H P C L
 3920 3940 3960
 GGGTCCCAGAGAGAAGGCTGGACAGACACCCAGGACTCCAATGTCTGCTCCCAGGGGC
 G P R E K A G Q T P Q D S N V C S P G A
 3980 4000 4020
 GCCGGCTGCTCACCCAGAGGGCCAGCCTCCCCAGAGCCAGAGTGCCAGGCCCGCAGCT
 P A A H P E G Q P P P E P E C P G P Q L
 4040 4060 4080
 CAACACGGGGACACAGCTGGTCCTCCAGCATGTGCAGGCGCTGCTGGTCAAGAGATTCCA
 N T G T Q L V L Q H V Q A L L V K R F Q
 4100 4120 4140
 ACACACCATCCGCAGCCACAAGGACTTCCTGGCGCAG|ATCGTGCTCCCGGCTACCTTTGT
 H T I R S H K D F L A Q I V L P A T F V
 4160 4180 4200
 GTTTTTGGCTCTGATGCTTTCTATTGTTATCCTTCCTTTTGGCGAATACCCCGCTTTGAC
 F L A L M L S I V I L P F G E Y P A L T
 4220 4240 4260
 CCTTACCCCTGGATATATGGGCAGCAGTACACCTTCTTCAG|CATGGATGAACCAGGCAG
 L H P W I Y G Q Q Y T F F S M D E P G S
 4280 4300 4320
 TGAGCAGTTCACGGTACTTGCAGACGTCCTCCTGAATAAGCCAGGCTTTGGCAACCGCTG
 E Q F T V L A D V L L N K P G F G N R C
 4340 4360 4380
 CCTGAAGGAAGGGTGGCTTCC|GGAGTACCCCTGTGGCAACTCAACACCCTGGAAGACTCC
 L K E G W L P E Y P C G N S T P W K T P
 4400 4420 4440
 TTCTGTGTCCCAAACATCACCCAGCTGTTCAGAAGCAGAAATGGACACAGGTCAACCC
 S V S P N I T Q L F Q K Q K W T Q V N P
 4460 4480 4500
 TTCACCATCCTGCAG|GTGCAGCACCAGGGAGAAGCTCACCATGCTGCCAGAGTGCCCCGA
 S P S C R C S T R E K L T M L P E C P E
 4520 4540 4560
 GGGTGCCGGGGCCTCCCGCCCCCAG|AGAACACAGCGCAGCACGGAAATTCTACAAGA
 G A G G L P P P Q R T Q R S T E I L Q D

FIG. 3E

4580 4600 4620
CCTGACGGACAGGAACATCTCCGACTTCTTGGTAAAAACGTATCCTGCTCTTATAAGAAG
L T D R N I S D F L V K T Y P A L I R S
4640 4660 4680
CAGC|TTAAAGAGCAAATTCTGGGTCAATGAACAGAG|GTATGGAGGAATTTCCATTGGAGG
S L K S K F W V N E Q R Y G G I S I G G
4700 4720 4740
AAAGCTCCCAGTCGTCCCCATCACGGGGGAAGCACTTGTGGGTTTTTAAGCGACCTTGG
K L P V V P I T G E A L V G F L S D L G
4760 4780 4800
CCGGATCATGAATGTGAGCGGG|GGCCCTATCACTAGAGAGGCCTCTAAAGAAATACCTGA
R I M N V S G G P I T R E A S K E I P D
4820 4840 4860
TTTCCTTAAACATCTAGAAACTGAAGACAACATTA|AGGTGTGGTTTAATAACAAAGGCTG
F L K H L E T E D N I K V W F N N K G W
4880 4900 4920
GCATGCCCTGGTCAGCTTTCTCAATGTGGCCACAACGCCATCTTACGGGCCAGCCTGCC
H A L V S F L N V A H N A I L R A S L P
4940 4960 4980
TAAGGACAGGAGCCCCGAGGAGTATGGAATCACCGTCATTAGCCAACCCCTGAACCTGAC
K D R S P E E Y G I T V I S Q P L N L T
5000 5020 5040
CAAGGAGCAGCTCTCAGAGATTACAGT|GCTGACCACTTCAGTGGATGCTGTGGTTGCCAT
K E Q L S E I T V L T T S V D A V V A I
5060 5080 5100
CTGCGTGATTTTCTCCATGTCCTTCGTCCCAGCCAGCTTTGTCCTTTATTTGATCCAGGA
C V I F S M S F V P A S F V L Y L I Q E
5120 5140 5160
GCGGGTGAACAAATCCAAGCACCTCCAGTTTATCAGTGGAGTGAGCCCCACCACCTACTG
R V N K S K H L Q F I S G V S P T T Y W
5180 5200 5220
GGTGACCAACTTCCTCTGGGACATC|ATGAATTATTCCGTGAGTGCTGGGCTGGTGGTGGG
V T N F L W D I M N Y S V S A G L V V G
5240 5260 5280
CATCTTCATCGGGTTTCAGAAGAAAGCCTACACTTCTCCAGAAAACCTTCCTGCCCTTGT
I F I G F Q K K A Y T S P E N L P A L V
5300 5320 5340
GGCACTGCTCCTGCTGTATGG|ATGGGCGGTCATTCCCATGATGTACCCAGCATCCTTCCT
A L L L L Y G W A V I P M M Y P A S F L
5360 5380 5400
GTTTGATGTCCCAGCACAGCCTATGTGGCTTTATCTTGTGCTAATCTGTTTCATCGGCAT
F D V P S T A Y V A L S C A N L F I G I
5420 5440 5460
CAACAGCAGTGCTATTACCTTCATCTTGAATTATTTGATAATAACCGG|ACGCTGCTCAG
N S S A I T F I L E L F D N N R T L L R
5480 5500 5520
GTTCAACGCCGTGCTGAGGAAGCTGCTCATTGTCTTCCCCCACTTCTGCCTGGGCCGGGG
F N A V L R K L L I V F P H F C L G R G

FIG. 3F

5540 5560 5580
CCTCATTGACCTTGCACTGAGCCAGGCTGTGACAGATGTCTATGCCCGGTTTG|GTGAGGA
L I D L A L S Q A V T D V Y A R F G E E
5600 5620 5640
GCACTCTGCAAATCCGTTCCACTGGGACCTGATTGGGAAGAACCTGTTTGCCATGGTGGT
H S A N P F H W D L I G K N L F A M V V
5660 5680 5700
GGAAGGGGTGGTGTACTTCCTCCTGACCCTGCTGGTCCAGCGCCACTTCTTCCTCTCCCA
E G V V Y F L L T L L V Q R H F F L S Q
5720 5740 5760
ATG|GATTGCCGAGCCCACTAAGGAGCCATTGTTGATGAAGATGATGATGTGGCTGAAGA
W I A E P T K E P I V D E D D D V A E E
5780 5800 5820
AAGACAAAGAATTATTACTGGTGGAAATAAACTGACATCTTAAGGCTACATGAACTAAC
R Q R I I T G G N K T D I L R L H E L T
5840 5860 5880
CAAG|ATTTATCTGGGCACCTCCAGCCCAGCAGTGGACAGGCTGTGTGTCGGAGTTCGCCC
K I Y L G T S S P A V D R L C V G V R P
5900 5920 5940
TGGAGAG|TGCTTTGGCCTCCTGGGAGTGAATGGTGCCGGCAAACAACCACATTCAAGAT
G E C F G L L G V N G A G K T T T F K M
5960 5980 6000
GCTCACTGGGGACACCACAGTGACCTCAGGGGATGCCACCGTAGCAGGCAAGAG|TATTTT
L T G D T T V T S G D A T V A G K S I L
6020 6040 6060
AACCAATATTTCTGAAGTCCATCAAATATGGGCTACTGTCCTCAGTTTGATGCAATCGA
T N I S E V H Q N M G Y C P Q F D A I D
6080 6100 6120
TGAGCTGCTCACAGGACGAGAACATCTTTACCTTTATGCCCGGCTTCGAGGTGTACCAGC
E L L T G R E H L Y L Y A R L R G V P A
6140 6160 6180
AGAAGAAATCGAAAAG|GTTGCAAACCTGGAGTATTAAGAGCCTGGGCCTGACTGTCTACGC
E E I E K V A N W S I K S L G L T V Y A
6200 6220 6240
CGACTGCCTGGCTGGCACGTACAGTGGGGGCAACAAGCGGAAACTCTCCACAGCCATCGC
D C L A G T Y S G G N K R K L S T A I A
6260 6280 6300
ACTCATTGGCTGCCACCGCTGGTGTCTGTG|GATGAGCCCACCACAGGGATGGACCCCA
L I G C P P L V L L D E P T T G M D P Q
6320 6240 6360
GGCACGCCGCATGCTGTGGAACGTCATCGTGAGCATCATCAGAAAAGGGAGGGCTGTGGT
A R R M L W N V I V S I I R K G R A V V
6380 6400 6420
CCTCACATCCCACAG|CATGGAAGAATGTGAGGCACTGTGTACCCGGCTGGCCATCATGGT
L T S H S M E E C E A L C T R L A I M V
6440 6460 6480
AAAGGGCGCCTTTCGATGTATGGGCACCATTGAGCATCTCAAGTCAA|ATTTGGAGATGG
K G A F R C M G T I Q H L K S K F G D G
6500 6520 6540
CTATATCGTCACAATGAAGATCAAATCCCCGAAGGACGACCTGCTTCCTGACCTGAACCC
Y I V T M K I K S P K D D L L P D L N P

FIG. 3G

6560 6580 6600
TGTGGAGCAGTTCTTCCAGGGGAACTTCCCAGGCAGTGTGCAGAGGGAGAGGCACTACAA
V E Q F F Q G N F P G S V Q R E R H Y N
6620 6640 6660
CATGCTCCAGTTCCAGGTCTCCTCCTCCTCCCTGGCGAGGATCTTCCAGCTCCTCCTCTC
M L Q F Q V S S S S L A R I F Q L L L S
6680 6700 6720
CCACAAGGACAGCCTGCTCATCGAGGAGTACTCAGTCACACAGACCACACTGGACCAG|GT
H K D S L L I E E Y S V T Q T T L D Q V
6740 6760 6780
GTTTGTAATTTTGCTAAACAGCAGACTGAAAGTCATGACCTCCCTCTGCACCCTCGAGC
F V N F A K Q Q T E S H D L P L H P R A
6800 6820 6840
TGCTGGAGCCAGTCGACAAGCCCAG|GACTGATCTTTCACACCGCTCGTTCCTGCAGCCAG
A G A S R Q A Q D
6860 6880 6900
AAAGGAACTCTGGGCAGCTGGAGGCGCAGGAGCCTGTGCCCATATGGTCATCCAAATGGA
6920 6940 6960
CTGGCCCAGCGTAAATGACCCCCTGCAGCAGAAAACAAACACACGAGGAGCATGCAGCG
6980 7000 7020
AATTCAGAAAGAGGTCTTTCAGAAGGAAACCGAAACTGACTTGCTCACCTGGAACACCTG
7040 7060 7080
ATGGTGAAACCAAACAATAACAAAATCCTTCTCCAGACCCCAGAACTAGAAACCCCGGGC
7100 7120 7140
CATCCCCTAGCAGCTTTGGCCTCCATATTGCTCTCATTTCAGCAGATCTGCTTTTCTG
7160 7180
CATGTTTGTCTGTGTGTCTGCGTTGTGTGTGATTTTCATGGAAA

FIG. 3H

Abc1 M A C X P Q L R L L L W K N L T F R R R Q T C Q L L L E V A W P L F I F L I L I S V R L S Y P P Y E 50
 ABCR M G F V R Q I Q L L L W K N W T L R K R Q K I R F V V E L V W P L S L F L V L I W L R N A N P L Y S 50
 Abc2
 ABCC M A V L R Q L A L L L W K N Y T L Q K R K V L V T V L E L F L P L L F S G I L I W L R L K I Q S E N 50

 Abc1 Q H E C H F P N K A M P S A G T L P W V Q G I I C N A N N P C F R Y P T P G E A P G V V G N F N K S 100
 ABCR H H E C H F P N K A M P S A G M L P W L Q G I F C N V N N P C F Q S P T P G E S P G I V S N Y N N S 100
 Abc2
 ABCC V P N A T I Y P G Q S I Q E L P L F F T F P P P G D T W E L A Y I P S H S D A A K T V T E T V R R A 100

 Abc1 I V S R L F S D A Q R L L L Y S Q R D T S I K D M H K V L R M L R Q I K H P N S N 141
 ABCR I L A R V Y R D F Q E L L M N A P E S Q H L G R I W T E L H I L S Q F M D T L R T H P E R I A G R G 150
 Abc2
 ABCC L V I N M R V R G F P S E K D F E D Y I R Y D N C S S S V L A A V V F E H P F N H S K E P L P L A V 150

 Abc1 L K L Q D F L V D N E T F S G F L Q H N L S L P R S T V D S L L Q X N V G L Q K V F L Q G Y Q L H L 191
 ABCR I R I R D I L K D E E T L T L F L I K N I G L S D S V V Y L L I N S Q V R P E Q F A H G V P D L A L 200
 Abc2
 ABCC K Y H L R F S Y T R R N Y M W T Q T G S F F L K E T E G W H 180

 Abc1 A S L . C N G S K L E E I I Q L G D A E V S A L C G L P R K K L D A A E R V L R Y N M D I 235
 ABCR K D I A C S E A L L E R F I I F S Q R R G A K T V R Y A L C S L S Q G T L Q W I E D T L Y A N V D F 250
 Abc2
 ABCC 180

 Abc1 L K . . . P V V T K L N S T S H L P T Q H L A E A T T V L L D S L G G L A Q E L F S T K S W S D M R 282
 ABCR F K L F R V L P T L L D S R S Q G I N L R . . . S W G G I L S D M S P R I Q E F I H R P S M Q D L L 297
 Abc2
 ABCC 180

 Abc1 Q E V M F L T N V N S S S S S T Q I Y Q A V S R I V C G H P E G G G L K I K S L N W Y E D N N Y K A 332
 ABCR W V T R P L M Q N G G P E T F T K L M G I L S D L L C G Y P E G G G S R V L S F N W Y E D N N Y K A 347
 Abc2
 ABCC 180

 Abc1 L F G G N N T E E D V D T F Y D N S T T P Y C N D L M K N L E S S P L S R I I W K A L K P L L V G K 382
 ABCR F L G I D S T R K D P I Y S Y D R R T T S F C N A L I Q S L E S N P L T K I A W R A A K P L L M G K 397
 Abc2
 ABCC 180

 Abc1 I L Y T P D T P A T R Q V M A E V N K T F Q E L A V F H D L E G M W E E L S P Q I W T F M E N S Q E 432
 ABCR I L Y T P D S P A A R R I L K N A N S T F E E L E H V R K L V K A W E E V G P Q I W Y F F D N S T Q 447
 Abc2
 ABCC 180

 Abc1 M D L V R T L L D S R G N D Q F W E Q K L D G L D W T A Q D I M A F L A K N P E D V Q S P N G S V Y 482
 ABCR M N M I R D T L G N P T V K D F L N R Q L G E E G I T A E A I L N F L Y K G P R E S Q A D D M A N F 497
 Abc2
 ABCC 180

 Abc1 T W R E A F N E T N Q A I Q T I S R F M E C V N L N K L E P I P T E V R L I N K S M E L L D E R K F 532
 ABCR D W R D I F N I T D R T L R L V N Q Y L E C L V L D K F E S Y N D E T Q L T Q R A L S L L E E N M F 547
 Abc2
 ABCC 180

 Abc1 W A G I V F T G I T P D S V E L P H H V K Y K I R M D I D N V E R T N K I K D G Y W D P G P R I A D P 582
 ABCR W A G V V F P D M Y P W T S S L P P H V K Y K I R M D I D V V E K T N K I K D R Y W D S G P R I A D P 597
 Abc2
 ABCC T T S L F P L F P N P G P R E P T 197

FIG. 4A

Abc1	F E D . . . M R Y V W G G F A Y L Q D V V E Q A I I R V L T G S E K K T G V Y V Q Q M P Y	624
ABCR	V E D . . . F R Y I W G G F A Y L Q D M V E Q G I T R S Q V Q A E A P V G I Y L Q Q M P Y	639
Abc2		0
ABCC	S P D G G E P G Y I R E G F L A V Q H A V D R A I M E Y H A D A A T R Q L F Q R L T V T I K R F P Y	247
Abc1	P C Y V D D I F L R V M S R S M P L F M T L A W I Y S V A V I I K S I V Y E K E A R L K E T M R I M	674
ABCR	P C F V D D S F M I I L N R C F P I F M V L A W I Y S V S M T V K S I V L E K E L R L K E T L K N Q	689
Abc2		0
ABCC	P P F i A D P F L V A i Q Y Q I P L L L L L S F T Y T A L T i A R A V V Q E K E R R L K E Y M R M M	297
Abc1	G L D N G I L W F S W F V S S L I P L L V S A G L L V V I L K L G N L L P Y S D P S V V F	719
ABCR	G V S N A V I W C T W F L D S F S I M S M S I F L L T I F I M H G R I L H Y S D P F I L F	734
Abc2		0
ABCC	G L S S W L H W S A W F L L F F L F L L i A A S F M T L L F C V K V K P N V A V L S R S D P S L V L	347
Abc1	V F L S V F A M V T I L Q C F L I S T L F S R A N L A A A C G G I I Y F T L Y L P Y V L C V A W Q D	769
ABCR	L F L L A F S T A T I M L C F L L S T F F S K A S L A A A C S G V I Y F T L Y L P H I L C F A W Q D	784
Abc2		0
ABCC	A F L L C F A i S T I S F S F M V S T F F S K A N M A A A F G G F L Y F F T Y I P Y F F V A P R Y N	397
Abc1	Y V G F S I K I F A S L L S P V A F G F G C E Y F A L F E E Q G I G V Q W D N L F E S P V E E D G F	819
ABCR	R M T A E L K K A V S L L S P V A F G F G T E Y L V R F E E Q G L G L Q W S N I G N S P T E G D E F	834
Abc2		0
ABCC	W M T L S Q K L C S C L L S N V A M A M G A Q L I G K F E A K G M G I Q W R D L L S P V N V D D D F	447
Abc1	N L T T A V S M M L F D T F L Y G V M T W Y I E A V F P G Q Y G I P R P W Y F P C T K S Y W F G E E	869
ABCR	S F L L S M Q M M L L D A A C Y G L L A W Y L D Q V F P G D Y G T P L P W Y F L L Q E S Y W L S G E	884
Abc2		0
ABCC	C F G Q V L G M L L L D S V L Y G L V T W Y M E A V F P G Q F G V P Q P W Y F F i M P S Y W C G K P	497
Abc1	G C S T R E E R A L E K T E P I D E K S H P G S S Q K G V S E I C M E E E P T H L R L G V S I Q N L	904
ABCR	G C S T R E E R A L E K T E P L T E E T E D P E H P E G I H D S F F E R E H P G W V P G V C V K N L	934
Abc2		32
ABCC	R A V A Q A C A M E S R H F E E T R G M E E E P T H L P L V V C V D K L	535
Abc1	V K V Y R D G M K . . V A V D G L A L N F Y E G Q I T S F L G H N G A G K T T T M S I L T G L F P P	952
ABCR	V K I F E P C G R . . P A V D R L N I T F Y E N Q I T A F L G H N G A G K T T T L S I L T G L L P P	982
Abc2		80
ABCC	S K V F R V G N K D R A A V R D L N L N L Y E G Q I T V L L G H N G A G K T T T L S M L T G L F P P	585
A		
Abc1	T S G T A Y I L G K D I R S E M S S I R Q N L G V C P Q H N V L F D M L T V E E H I W F Y A R L K G	1002
ABCR	T S G T V L V G G R D I E T S D A V R Q S L G M C P Q H N I L F H H L T V A E H M L F Y A Q L K G	1032
Abc2		130
ABCC	T S G S A T I Y G H D I R T E M D E I R K N L G M C P Q H N V L F D R L T V E E H L W F Y S R L K S	635
Abc1	L S E K H V K A E M E Q M A L D V G L P P S K L K S K T S Q L S G G M Q R K L S V A L A F V G G S K	1052
ABCR	K S Q E E A Q L E M E A M L E D T G L H H . K R N E E A Q D L S G G M Q R K L S V A I A F V G D A K	1081
Abc2		179
ABCC	L S R Q K C P E E V K Q M L H I I G L E D . K W N S R S R F L S G G M R R K L S I G I A L I A G S K	684
C		
Abc1	V V I L D E P T A G V D P Y S R R G I W E L L L K Y R Q G R T I I L S T H H M D E A D I L G D R I A	1102
ABCR	V V I L D E P T S G V D P Y S R R S I W D L L L K Y R S G R T I I M P T H H M D E A D H Q G D R I A	1131
Abc2		229
ABCC	A I I L D E P T A G V D P Y A R R A I W D L I L K Y K P G R T I L L S T H H M D E A D L L G D R I A	734
B		
Abc1	I I S H G K L C G V G S S L F L K N Q L G T G Y Y L T L V K K D V E S S L S S C R N S S S T V S C L	1152
ABCR	I I A Q G R L Y C S G T P L F L K N C F G T G L Y L T L V R K . M K N I Q S Q R K G S E G T C S C S	1180
Abc2		279
ABCC	I M A K G E L Q C C G S S L F L K Q K Y G A G Y H M T L V K E P	766

FIG. 4B

Abc1	K K E D S V S Q S S S D A G L G S D H E S D T L T I D V S A I S N L I R K H V S E A R L V E D I G H	1202
ABCR	S K G F S T C P A H V D D L T P E . . . Q V L D G D V N E L M D V I R L H H V V P E A A R L V E C T I G Q	1227
Abc2	P R L S S C S E P H C N P E D I S Q L V H H V V P A S S A T L E S S A G A	309
ABCC	792
Abc1	E L I T Y V L P Y E A A K E G A E V E L F H E I D R L S D L G I S S Y G I S E T T L E E E I F L K V I A	1252
ABCR	E L I F L L P N K N A F K H R G A Y A S L F F R E Q L E H S L L A D L G L S S S F G I S E D T P L E E E I F L K V I T	1277
Abc2	E L I S Y I L P S R E S A V K K G A F F E R L F F Q Q L E E H S L L A D L G L S S S F G I S E D T P L E E E I F L K V I S	359
ABCC	E L I S F I L P R E S T H R . . . F E G L F F A K L E K K Q K E L G I A S F G A S I T T M E E E V F L R V G	840
Abc1	E E S G V D A E T S D G T L P A R R N R . R A F G D K Q . S C	1281
ABCR	E D D Q S L E N S E A D V K E S R K D V L P S D S G E P L T A G G G Q A G N L A R C S E S E L A Q S Q . P C	1303
Abc2	E D D Q S L E N S E A D V K E S R K D V L P S D S G E P L T A G G G Q A G N L A R C S E S E L A Q S Q . P C	408
ABCC	K L V D S S M D I Q A I Q L P A L Q Y Q H E R R A S D W A V D S N L C G A	877
Abc1	L H P F T E D D A V D P N D S S D I D P E S R E T D L L S G M D	1312
ABCR	L G P P R E K A G S A R G E E G T G Y S D G Y G D Y R P L F D N L Q D P D N V S L Q E A E M E A L A Q	1238
Abc2	L Q S A S S V G S A R G E E E T	458
ABCC	M D P S D G I G A L I E E E R T	893
Abc1	. G K G S Y Q L K G W K L T Q Q E V A L L W K R L L I A R R S R K G F F A Q I V L P A V F V C I A	1361
ABCR	. C P G P Q L N T G T Q L V L Q H V Q A L L V K R R F H C A Y S W R R S H K G F F A Q I V L P A V F V C I A	1387
Abc2	V G Q G S R K L T G W W L L K M R Q F H G L L V K R F H C A Y S W R R S H K G F F A Q I V L P A V F V C I A	508
ABCC	. . . A V K L N T G L A L H C Q Q F W A M F L K R A A Y S W R E W K M V A A Q V L V P L T C V T L A	940
H1		
Abc1	L V F S L I V P P F G K Y P S L E L L Q P W M Y N E Q Y T F . V S N	1393
ABCR	M L S I S V I P P F F G G D L P P M L L T L L Q P P W M Y N E Q Y T F . V S N	1419
Abc2	N T V A L S V I P P F F G G D L P P M L L T L L Q P P W M Y N E Q Y T F . V S N	558
ABCC	L L A I N Y S S E L F D D P M L L T L L Q P P W M Y N E Q Y T F . V S N	940
Abc1	D A P E D M G T Q E L L N A L T K D P G F F	1414
ABCR	D E S P Q Q L V S T F R L P S G V G A T C V L K S P P A N G S Q L G Q Q L L L L A A R F F	1440
Abc2	D A S P Q Q L V S T F R L P S G V G A T C V L K S P P A N G S Q L G Q Q L L L L A A R F F	608
ABCC F S V P P A N G S Q L G Q Q L	982
Abc1	G T R C M E G N P I P D T P C L A G E E D W T I S P V P Q S I V D L F Q N G N W T M K N P S	1460
ABCR	G N R C L K E G W L P E Y P C G N S T P W K T P S S P V P Q S I V D L F Q N G N W T M K N P S	1485
Abc2	D S M C L E S F T Q G L P L S N F V P P P S P A P S D S P V P Q S I V D L F Q N G N W T M K N P S	658
ABCC	982
Abc1	P A C Q C S S D K I K K M L P V C P P G A G G L P P P Q R K Q K T A D I	1496
ABCR	P S C R C S S T R E K L L T M L P E P V R C T C S A Q G T G F S C P E S S A G G L P P P Q R T Q R S T E I	1521
Abc2	P E T W T S A P S L P R L V H E P V R C T C S A Q G T G F S C P S S V G G L H P P Q M R V V T G D I	707
ABCC S E H L K D A L Q A E G Q E P R E V	1000
Abc1	L Q N L T G R N I S D Y L V K T Y V Q I I A K S L K N K I W V N E F R Y G G F S L G V S N S Q A L P	1546
ABCR	L Q D L T D R N N I S D F L V K T T Y P A L I R S S L K S K F W V N E Q R Y G G I S I G G K L P V V P I	1571
Abc2	L T D T G H N N V S E Y L L F T S D R F R L H . R Y G A I T F G N	739
ABCC	L G D L E E F L I F R A S V E G G F N E R C L	1024
Abc1	P S H E V N D A I K Q M K K L L K L T K D T S A D R F L S S L G R F M A G L D T K N N V K V W F N N	1596
ABCR	T G E A L V G F L S D L G R I M N V S G G P I T R E A S F A S K E I P D F L K H L D E T E D N I K V W F N N	1621
Abc2 V Q K S I P A S F G A R V P P M V R K I A V R R V A Q V L Y N N	771
ABCC V A A S F R D V G E R T V V N A L F N N	1044
Abc1	K G W H A I S S F L N V I N N A I L R A N L Q K G E . N S P S Q Y G T I T A F N H P L N L I T K Q L S E	1645
ABCR	K G W H A L V S F F L N V A H N A I L R A N L Q P K G D R . N S P P E A Y X I T T V I S Q P L N L I T K E Q L S E	1670
Abc2	K G Y H S M P T Y L N S L N N A I L R A N L Q P K S K G N P A A Y X I T T V I T T N H P M N K I S A S L S	820
ABCC	Q A Y H S P A T A L A V V D N L L F K L L C G P H A S I V V S N F P Q P R S A L Q A A K	1088
Abc1	V A L M T T S V D V L V S I C V I F A M S F V P A S F V V L I Q E R V S K A K H L Q F I S G V K P	1695
ABCR	I T V L T T S V D A V V A I C V I F S M S F V P A S F V V L Y L I Q E R V N K S K H L Q F I S G V S P P	1720
Abc2	L D Y L L Q G T D V V I A I F I L V A M S F V P A S F V V F L V A S E R V S T K A K H L Q F V S G C N P	870
ABCC	D Q F N E G R K G F D I A L N L L F A M A F L A S T F S I L A V S E R A V Q A K H V Q F V S G V H V	1138

FIG. 4C

Abc1	V I Y W L S N F V W D M C N Y V V P A T L V I I T I C F Q K S Y V S S T N L P V L A L L L L L Y	1745
ABCR	T T Y W V T N F L W D I M N Y S V S A G L V V G I F I G F F Q K K A Y T S S P E T N L P A V L S L L L L Y	1770
Abc2	V I Y W L S N F V W D M C N Y V V P A T L V I I T I C F Q K S Y V S S T N L P V L A L L L L L Y	920
ABCC	A S F W L S A L L W D L I S F L I P S L L L L V V F K A F D V R A F I R D G H M A D T L L L L L L Y	1188
Abc1	G W S A T I P L M Y P A S F V F K I P S T A Y V V L T S V N L F I G I N G S S V A T F F V L F E L F T N N K	1795
ABCR	G W S A T I P L M Y P A S F F L F F D E V P S T A Y V V I A L S C A N L F F I G I N S S A I T F F L F E L F D N N R	1820
Abc2	G W S A T I P L M Y P A S F F W F F E V P S S A Y V V F L I V I N L F F I G I T A T V A T F L F E L F F E H D K	970
ABCC	G W A T I P L M Y L M N F F F L G A A T A Y T R L T I F N I L S G I A T F L M V T I M R I . . P A V	1236
Abc1	L N D I N D I L K S V F L I F P H F C L G R G L I D M V K N Q A M A D A L E R	1834
ABCR	L L R F N I L K S C F L I F P H F C L G R G L I D M V K N Q A M A D A L E R	1860
Abc2	L L R F N I L K S C F L I F P H F C L G R G L I D M A Y N E Y I N E Y Y A K	1010
ABCC	K L E L S K T L D H V F L V L P N H C L G M A V S S F Y E N Y E T R R Y C T S S E V A A H Y C K K	1286
Abc1	F G . E . N R F V S P L S W D L V G R N L F A M A V E G V V F F L I T V L I Q Y R F F I R P R P V K	1882
ABCR	F G . E . F H S A N S P F F H W D L T G K N L F A M A V T E G G V V F F L I T L L V Q R H F F L S Q W I A E	1898
Abc2	I G . Q F D K M K S P F F F W D I V T R G L V A M T V E G G V V F F L I T L M C Q Y N F L R Q P Q R L P	1059
ABCC	Y N I Q Y Q E N F Y A W S A P G V G R F V A S M A A S G C A Y L I L F L I E T N L L Q R L R G I L	1336
Abc1	A K L P P L N D E D E D V R R E E R Q R I L D G G G N D I . . . L E K E L	1917
ABCR	P T K K P I V D E D D V A S E E R Q R I L D G G G N D I . . . L R H E L	1943
Abc2	V S T K P V V E D D V A S E E R Q R I L D G G G N D I . . . V K E N L	1093
ABCC	C A L R R R R T L T E L Y T R M P V L P E D Q D V A D E E R T R I L A P S P D S L L H T P I K E L	1386
Abc1	T K I Y R R K R K P . . . A V D R I C I G I . P P G E C F G L L G V N G A G K S T I F K M L T G D I	1963
ABCR	T K I Y R R K R K P . . . A V D R L C C I V G V . P P G E C F G L L G V N G A G K T I F K M L T G D I	1989
Abc2	T K I Y R R K R K P . . . A V D R L C C I V G V . P P G E C F G L L G V N G A G K T I F K M L T G D I	1143
ABCC	S K V Y E Q R . . V P L L A V D R L S L A V . Q K G E C F G L L G F N G A G K T I F K M L T G E E	1433
A		
Abc1	P V T R G D A F L N K N S I L L S N I H E V H Q N M G Y C P Q F D A I T E L L T G R E H V E F F A R L	2013
ABCR	S T T G G D A F L N K N S I L L S N I H E V H Q N M G Y C P Q F D A I T E L L T G R E H V E F F A R L	2039
Abc2	S T T G G D A F L N K N S I L L S N I H E V H Q N M G Y C P Q F D A I T E L L T G R E H V E F F A R L	1193
ABCC	S L T S G D A F V G G H S V L S S D V G K V R Q R I G Y C P Q F D A I L D H M T G R E N L V M Y A R L	1483
Abc1	R G V P E K E V G K F G E W A I R K L G L V K Y G E K Y A S N Y S G G N K R K L S T A M A L I G G P	2063
ABCR	R G V P E K E V G K F G E W A I R K L G L V K Y G E K Y A S N Y S G G N K R K L S T A M A L I G G P	2080
Abc2	R G V P E K E V G K F G E W A I R K L G L V K Y G E K Y A S N Y S G G N K R K L S T A M A L I G G P	1243
ABCC	R G I P E R H I G A C V E N T L R G L L L E P H A N K L V R T Y S G G N K R K L S T G I A L I G E P	1533
C		
Abc1	P V V F L D E P T T G M D P K A R R R F L W N C A L S I V K E G R S V V L T S H S M E E C E A L C T R	2113
ABCR	P L V F L D E P T T G M D P K A R R R F L W N C A L S I V K E G R S V V L T S H S M E E C E A L C T R	2139
Abc2	A F I F L D E P T T G M D P K A R R R F L W N C A L S I V K E G R S V V L T S H S M E E C E A L C T R	1293
ABCC	A V I F L D E P S T G M D P V A R R R L L W D T V A R A R E S G K A I T I T S H S M E E C E A L C T R	1583
B		
Abc1	M A I M V N G R F R C L G S V Q H L K N R F G D G Y T I V V R I A G S N D D L L P D L K P V Q E F F	2159
ABCR	L A I M V N G R F R C L G S V Q H L K N R F G D G Y T I V V R I A G S N D D L L P D L K P V Q E F F	2189
Abc2	L A I M V N G R F R C L G S V Q H L K N R F G D G Y T I V V R I A G S N D D L L P D L K P V Q E F F	1338
ABCC	L A I M V Q G Q F K C L G S P Q H L K S K F G S G Y S L R A K V Q S E G Q Q . . E A L E E F K A F V	1631
Abc1	G L A F P G S V L K E K H R N M L Q Y Q L P S S L S S L A R I F F S I L S Q S H K K R L H I E D Y S V S	2209
ABCR	Q G N F P G S V L K E K H R N M L Q Y Q L P S S L S S L A R I F F S I L S Q S H K K R L H I E D Y S V S	2237
Abc2	N R N F P E A H A Q G K T P Y K V Q Y Q L K S E H I S L A Q V F S K M L E Q V V G V L G I E D Y S V S	1388
ABCC	D L T F P G S V L E D E H I Q G M V H Y H L P G R D L S W A K V F G I L E K A K E K Y G V D D Y S V S	1631
Abc1	Q T T L D Q V F V N F A K D Q S D D D H L K D L S L H K N Q T V V D V A V	2246
ABCR	Q T T L D Q V F V N F A K D Q S D D D H L K D L S L H P R A A G A S R Q A	2271
Abc2	Q T T L D N V F V N F A K K Q S D N V E Q Q E A E P S S L P S P L G L L S L L R P R P A P T E L R A	1438
ABCC	Q I S L E T Q V F L S F A H L Q P T A E E G R L R P R P A P T E L R A	1704
Abc1	L T S F L Q D E K V K E S Y V	2261
ABCR	Q D	2273
Abc2	L V A D E P E D L D T E D E G L I S F E E E R A Q L S F N T D T L C	1472
ABCC	1704

FIG. 4D

MAPPING THE MOUSE *ABCR* LOCUS

Jackson BSS
Chromosome 3

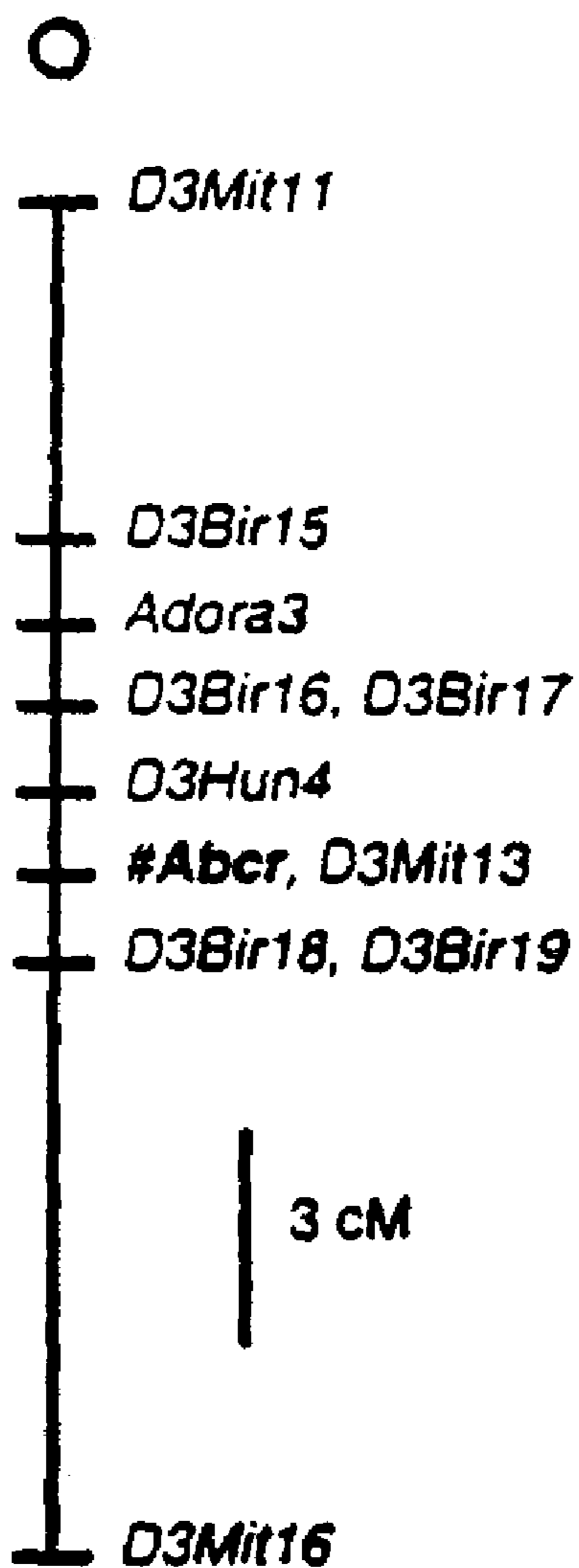


FIG. 5

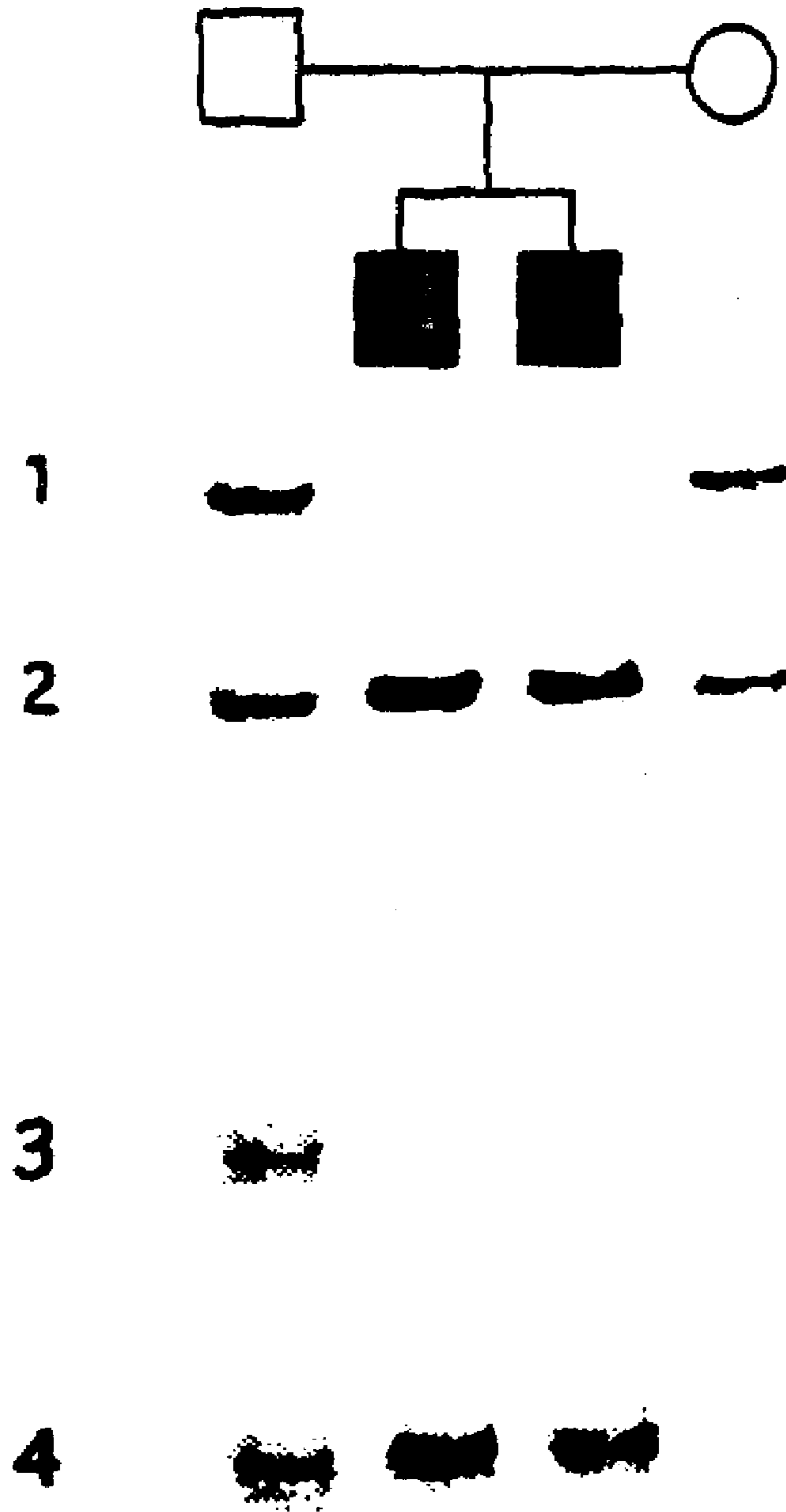


FIG. 6

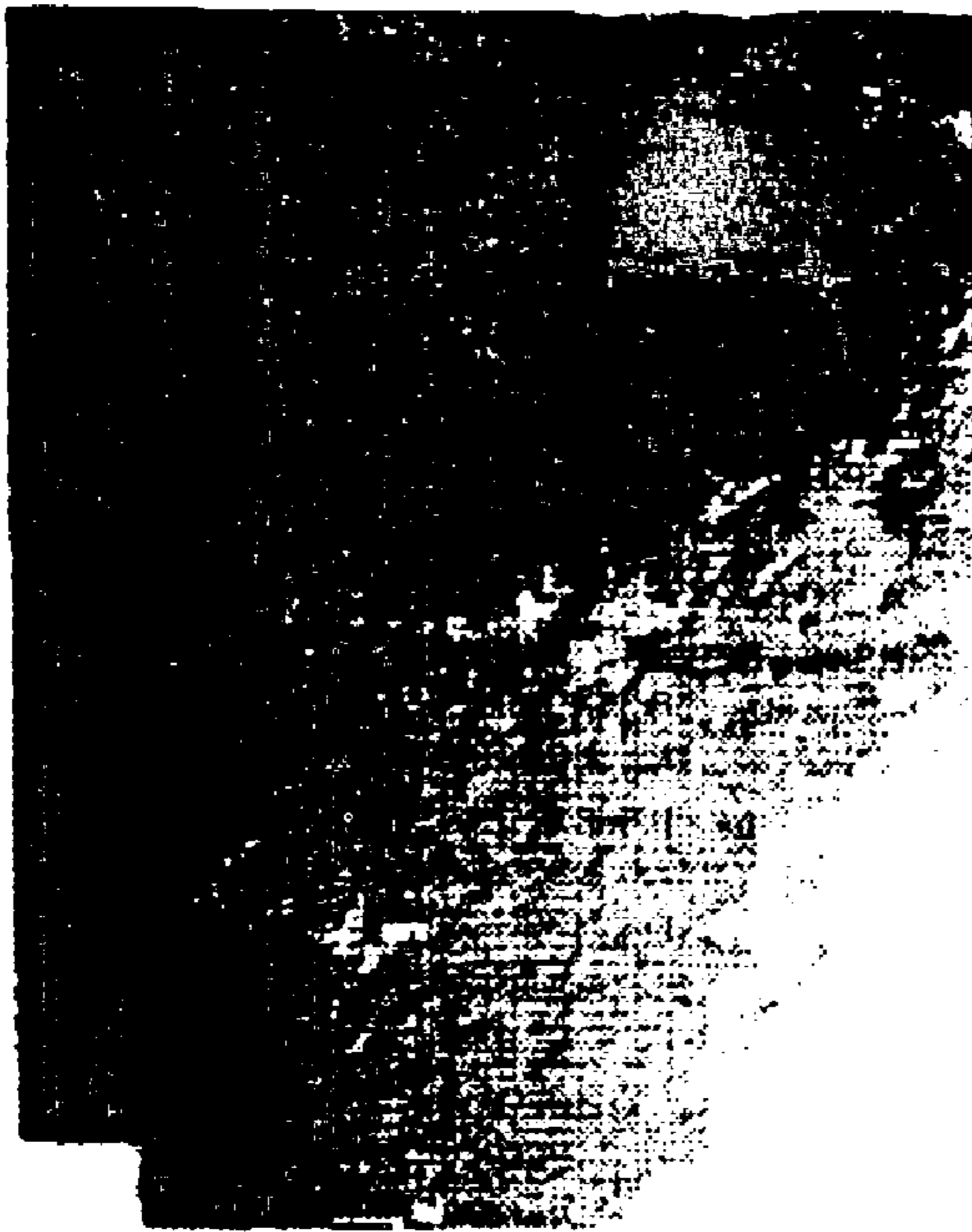


FIG. 7A

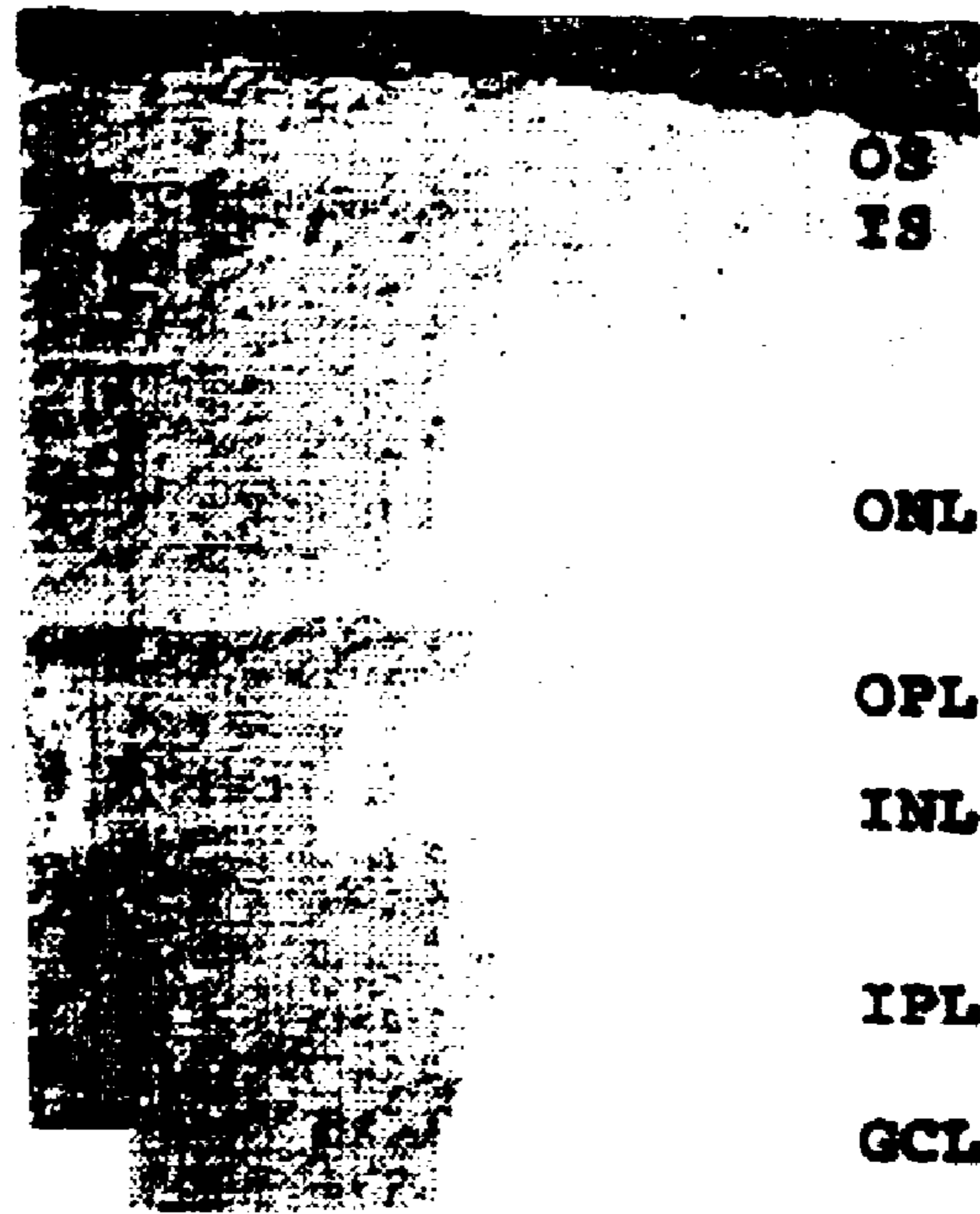


FIG. 7B



FIG. 7C

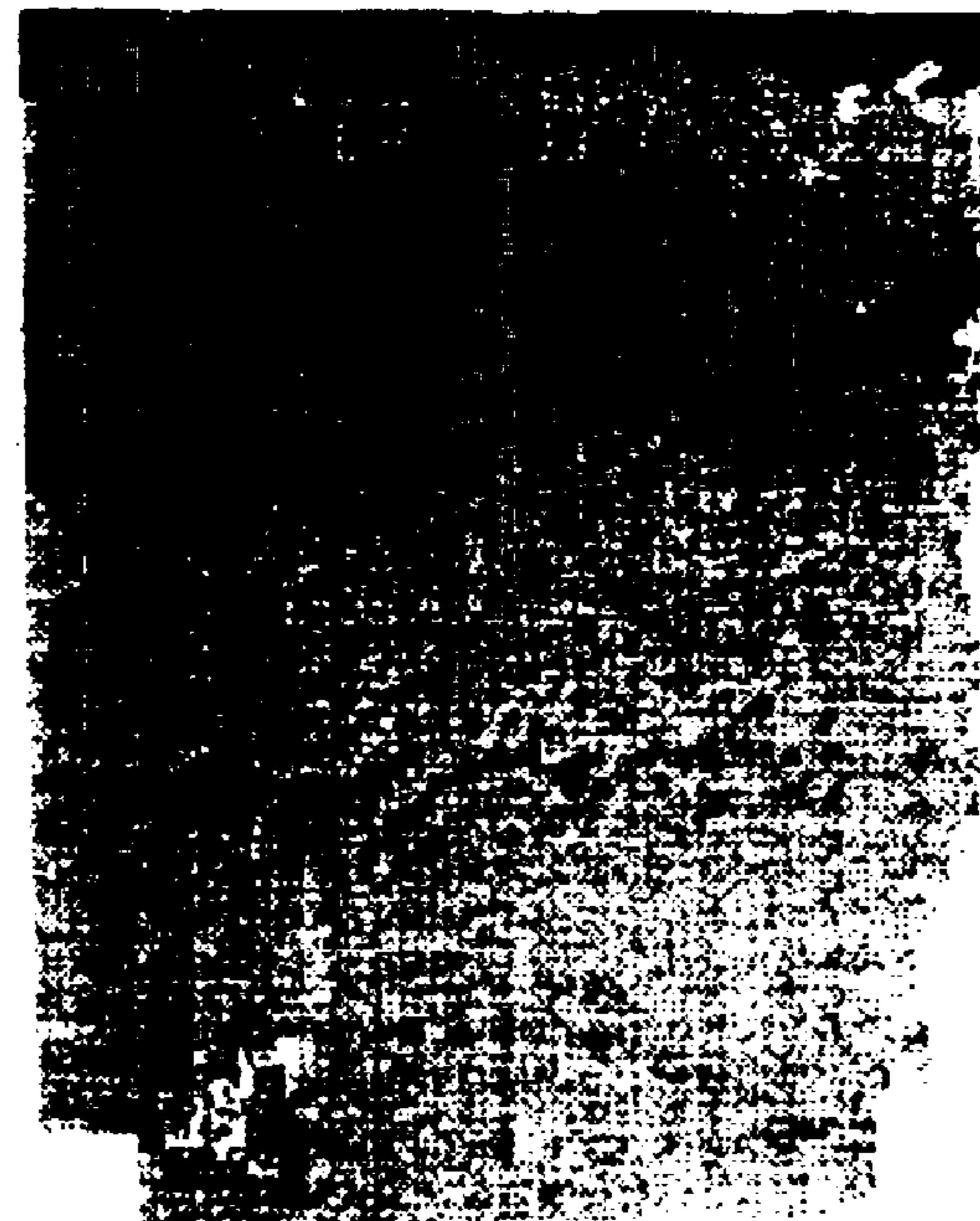


FIG. 7D

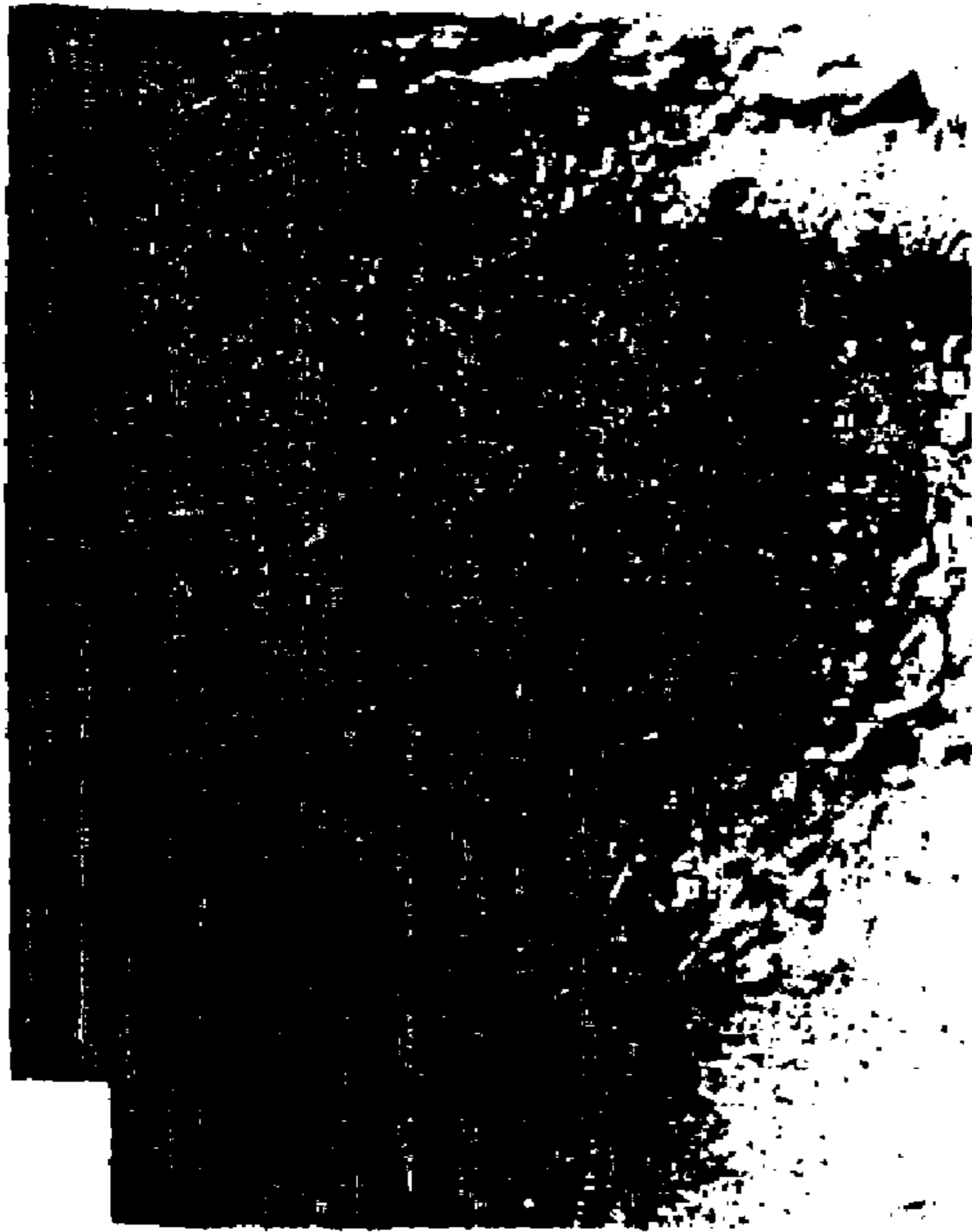


FIG. 7E



FIG. 7F

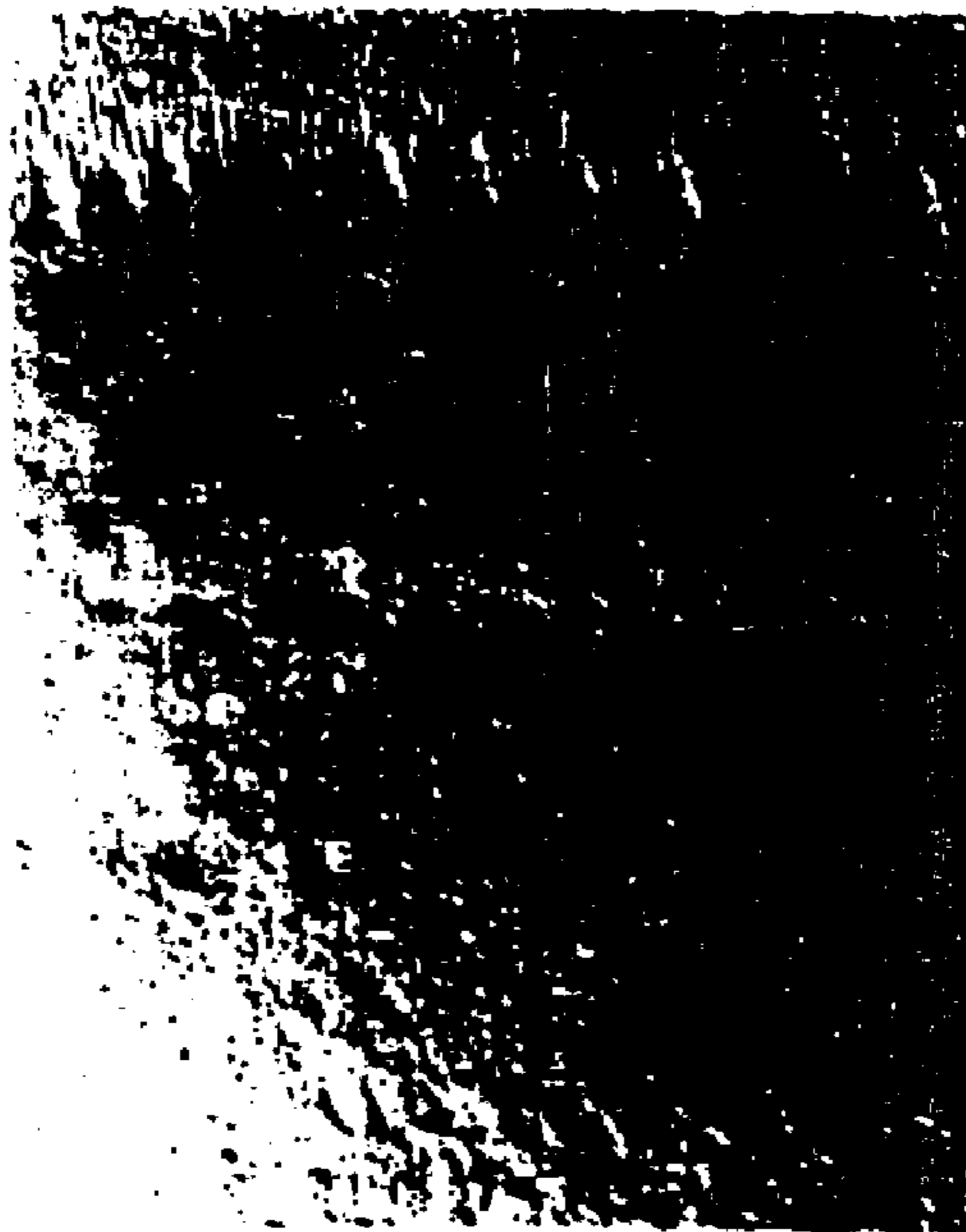


FIG. 7G

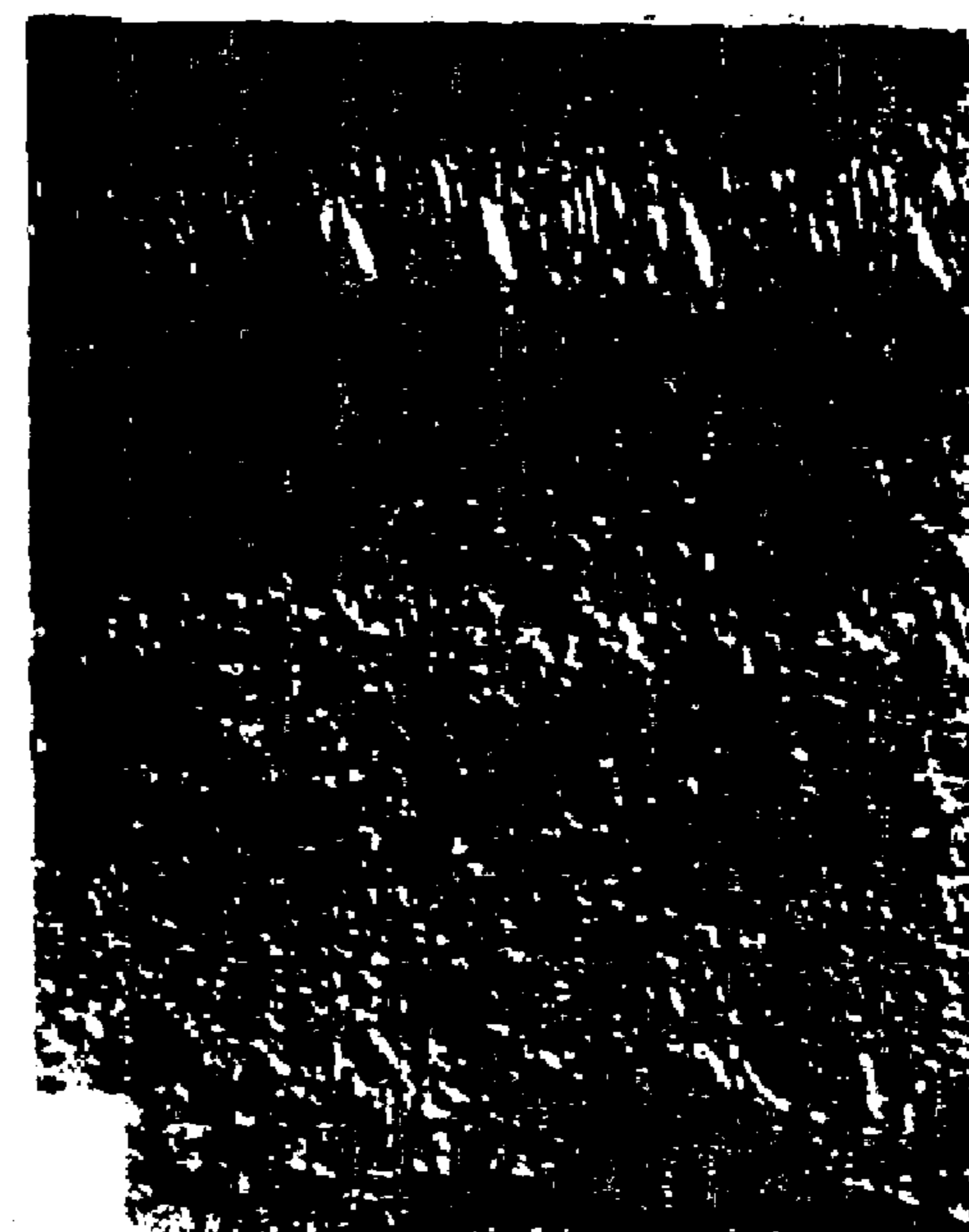
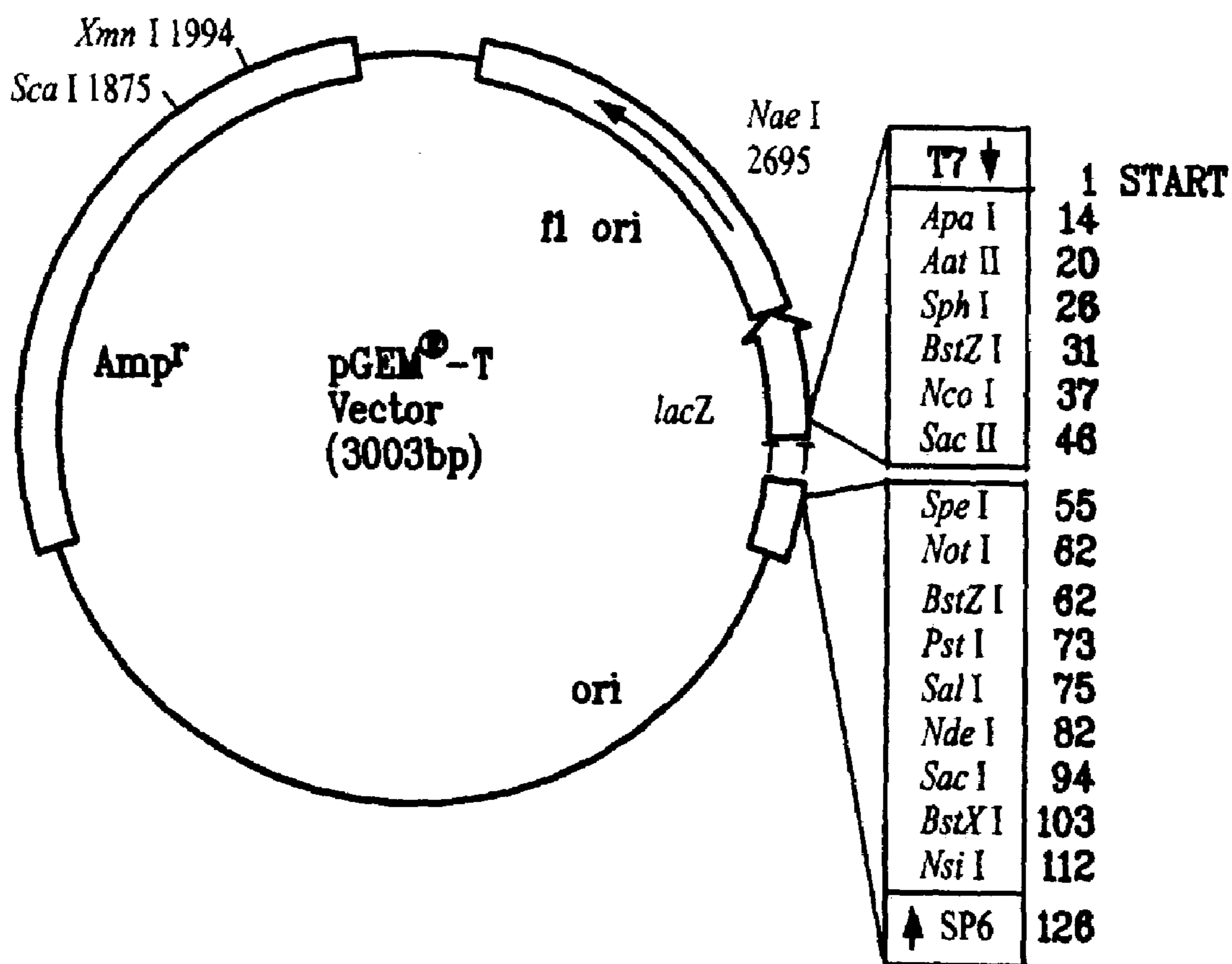


FIG. 7H

FIG. 8



**NUCLEIC ACID AND AMINO ACID
SEQUENCES FOR ATP-BINDING CASSETTE
TRANSPORTER AND METHODS OF
SCREENING FOR AGENTS THAT MODIFY
ATP-BINDING CASSETTE TRANSPORTER**

CROSS-REFERENCE TO RELATED
APPLICATIONS

This application is a continuation application of and claims priority to U.S. non-provisional application Ser. No. 09/032,438, filed Feb. 27, 1998 now U.S. Pat. No. 6,713,300, and benefit of U.S. provisional application Ser. No. 60/039,388, filed Feb. 27, 1997. Each of these applications is hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY
SPONSORED RESEARCH

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BACKGROUND OF THE INVENTION

Macular degeneration affects approximately 1.7 million individuals in the U.S. and is the most common cause of acquired visual impairment in those over the age of 65. Stargardt disease (STGD; McKusick Mendelian Inheritance (MIM) #248200) is arguably the most common hereditary recessive macular dystrophy and is characterized by juvenile to young adult onset, central visual impairment, progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, and the frequent appearance of orange-yellow flecks distributed around the macula and/or the midretinal periphery (Stargardt, 1909; Anderson et al., 1995). A clinically similar retinal disorder (Fundus Flavimaculatus, FFM, Franceschetti, 1963) often displays later age of onset and slower progression (Fishman, 1976; Noble and Carr, 1979). From linkage analysis, it has been concluded that STGD and FFM are most likely allelic autosomal recessive disorders with slightly different clinical manifestations caused by mutation(s) of a gene at chromosome 1p13-p21 (Gerber et al., 1995; Anderson et al., 1995). The STGD gene has been localized to a 4 cM region flanked by the recombinant markers D1S435 and D1S236 and a complete yeast artificial chromosome (YAC) contig of the region has been constructed (Anderson et al., 1995). Recently, the location of the STGD/FFM locus on human chromosome 1p has been refined to a 2 cM interval between polymorphic markers D1S406 and D1S236 by genetic linkage analysis in an independent set of STGD families (Hoyng et al., 1996). Autosomal dominant disorders with somewhat similar clinical phenotypes to STGD, identified in single large North American pedigrees, have been mapped to chromosome 13q34 (STGD2; MIM #153900; Zhang et al., 1994) and to chromosome 6q11-q14 (STGD3; MIM #600110; Stone et al., 1994), although these conditions are not characterized by the pathognomonic dark choroid observed by fluorescein angiography (Gass, 1987).

Members of the superfamily of mammalian ATP binding cassette (ABC) transporters are being considered as possible candidates for human disease phenotypes. The ABC superfamily includes genes whose products are transmembrane

proteins involved in energy-dependent transport of a wide spectrum of substrates across membranes (Childs and Ling, 1994; Dean and Allikmets, 1995). Many disease-causing members of this superfamily result in defects in the transport of specific substrates (CFTR, Riordan et al., 1989; ALD, Mosser et al., 1993; SUR, Thomas et al., 1995; PMP70, Shimozawa et al., 1992; TAP2, de la Salle et al., 1994). In eukaryotes, ABC genes encode typically four domains that include two conserved ATP-binding domains (ATP) and two domains with multiple transmembrane (TM) segments (Hyde et al. 1996). The ATP-binding domains of ABC genes contain motifs of characteristic conserved residues (Walker A and B motifs) spaced by 90–120 amino acids. Both this conserved spacing and the “Signature” or “C” motif just upstream of the Walker B site distinguish members of the ABC superfamily from other ATP-binding proteins (Hyde et al., 1990; Michaelis and Berkower, 1995). These features have allowed the isolation of new ABC genes by hybridization, degenerate PCR, and inspection of DNA sequence databases (Allikmets et al., 1993, 1995; Dean et al., 1994; Luciani et al., 1994).

The characterization of twenty-one new members of the ABC superfamily may permit characterization and functions assigned to these genes by determining their map locations and their patterns of expression (Allikmets et al., 1996). That many known ABC genes are involved in inherited human diseases suggests that some of these new loci will also encode proteins mutated in specific genetic disorders. Despite regionally localizing a gene by mapping, the determination of the precise localization and sequence of one gene nonetheless requires choosing the certain gene from about 250 genes, four to about five million base pairs, from within the regionally localized chromosomal site.

While advancements have been made as described above, mutations in retina-specific ABC transporter (ABCR) in patients with recessive macular dystrophy STGD/FFM have not yet been identified to Applicant’s knowledge. That ABCR expression is limited to photoreceptors, as determined by the present invention, provides evidence as to why ABCR has not yet been sequenced. Further, the ABC1 subfamily of ABC transporters is not represented by any homolog in yeast (Michaelis and Berkower, 1995), suggesting that these genes evolved to perform specialized functions in multicellular organisms, which also lends support to why the ABCR gene has been difficult to identify. Unlike ABC genes in bacteria, the homologous genes in higher eukaryotes are much less well studied. The fact that prokaryotes contain a large number of ABC genes suggests that many mammalian members of the superfamily remain uncharacterized. The task of studying eukaryote ABC genes is more difficult because of the significantly higher complexity of eukaryotic systems and the apparent difference in function of even highly homologous genes. While ABC proteins are the principal transporters of a number of diverse compounds in bacterial cells, in contrast, eukaryotes have evolved other mechanisms for the transport of many amino acids and sugars. Eukaryotes have other reasons to diversify the role of ABC genes, for example, performing such functions as ion transport, toxin elimination, and secretion of signaling molecules.

Accordingly, there remains a need for the identification of the sequence of the gene, which in mutated forms is associated with retinal and/or macular degenerative diseases, including Stargardt Disease and Fundus Flavimaculatus, for example, in order to provide enhanced diagnoses and improved prognoses and interventional therapies for individuals affected with such diseases.

SUMMARY OF THE INVENTION

The present invention provides sequences encoding an ATP binding cassette transporter. Nucleic acid sequences, including SEQ ID NO: 1 which is a genomic sequence, and SEQ ID NOS: 2 and 5 which are cDNA sequences, are sequences to which the present invention is directed.

A further aspect of the present invention provides ATP binding cassette transporter polypeptides and/or proteins. SEQ ID NOS: 3 and 6 are novel polypeptides of the invention produced from nucleotide sequences encoding the ATP binding cassette transporter. Also within the scope of the present invention is a purified ATP binding cassette transporter.

The present invention also provides an expression vector comprising a nucleic acid sequence encoding an ATP binding cassette transporter, a transformed host cell capable of expressing a nucleic acid sequence encoding an ATP binding cassette transporter, a cell culture capable of expressing an ATP binding cassette transporter, and a protein preparation comprising an ATP binding cassette transporter.

The present invention is also directed to a method of screening for an agent that modifies ATP binding cassette transporter comprising combining purified ATP binding cassette transporter with an agent suspected of modifying ATP binding cassette transporter and observing a change in at least one characteristic associated with ATP binding cassette transporter. The present invention provides methods of identifying an agent that inhibits macular degeneration comprising combining purified ATP binding cassette transporter from a patient suspected of having macular degeneration and an agent suspected interacting with the ATP binding cassette transporter and observing an inhibition in at least one of the characteristics of diseases associated with the ATP binding cassette transporter. In addition, the present invention provides for methods of identifying an agent that induces onset of at least one characteristic associated with ATP binding cassette transporter comprising combining purified wild-type ATP binding cassette transporter with an agent suspected of inducing a macular degenerative disease and observing the onset of a characteristic associated with macular degeneration.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A and 1B displays the ABCR gene and amplification products. FIG. 1A displays a physical map of the ABCR gene. Mega-YAC clones from the CEPH mega-YAC genomic library (Bellane-Chantelot et al., 1992) encompassing the 4cM critical region for STGD are represented by horizontal bars with shaded circles indicating confirmed positives for STSs by landmark mapping. The individual STS markers and their physical order are shown below the YACs with arrows indicating the centromeric (cen) and telomeric (1pter) direction (Anderson et al., 1995). The horizontal double head arrow labeled STGD indicates the refined genetic interval delineated by historical recombinants (Anderson et al., 1995). FIG. 1B displays the results of agarose gel electrophoresis of PCR amplification products with primers from the 5' (GGTCTTCGTGTGGTTCATT, SEQ ID NO: 114, GGTCCAGTTCTCCAGAG, SEQ ID NO: 115, labeled 5' ABCR) or 3' (ATCCTCTGACTCAGCAATCACA, SEQ ID NO: 116, TTGCAATTACAAATGCAATGG, SEQ ID NO: 117, labeled 3' ABCR) regions of ABCR on the 13 different YAC DNA templates indicated as diagonals above the gel. The asterisk denotes that YAC 680_b_5 was positive for the 5' ABCR PCR but negative for

the 3' ABCR PCR. These data suggest the ABCR gene maps within the interval delineated by markers D1S3361–D1S236 and is transcribed toward the telomere, as depicted by the open horizontal box.

FIG. 2 exhibits the size and tissue distribution of ABCR transcripts in the adult rat. A blot of total RNA from the indicated tissues was hybridized with a 1.6 kb mouse *Abcr* probe (top) and a ribosomal protein S26 probe (bottom; Kuwano et al., 1985). The ABCR probe revealed a predominant transcript of approximately 8 kb that is found in retina only. The mobility of the 28S and 18S ribosomal RNAs are indicated at the right. B, brain; H, heart; K, kidney; Li, liver; Lu, lung; R, retina; S, spleen.

FIGS. 3A–H shows the sequence of the ABCR coding region within the genomic ABCR sequence, SEQ ID NO: 1. The sequence of the ABCR cDNA, SEQ ID NO: 2, is shown with the predicted protein sequence, SEQ ID NO: 3, in one-letter amino acid code below. The location of splice sites is shown by the symbol |.

FIGS. 4A–D displays the alignment of the ABCR protein, SEQ ID NO:3, with other members of the ABC1 subfamily. The deduced amino acid sequence of ABCR is shown aligned to known human and mouse proteins that are members of the same subfamily. *Abc1*, mouse *Abc1* (SEQ ID NO:118); *Abc2*, mouse *Abc2* (SEQ ID NO:119); and *ABCC*, human *ABC* gene (SEQ ID NO:120). The Walker A and B motifs and the Signature motif C are designated by underlining and the letters A, B, and C, respectively.

FIG. 5 exhibits the location of *Abcr* from a Jackson BSS Backcross showing a portion of mouse chromosome 3. The map is depicted with the centromere toward the top. A 3 cM scale bar is also shown. Loci mapping to the same position are listed in alphabetical order.

FIG. 6 shows the segregation of SSCP variants in exon 49 of the ABCR gene in kindred AR293. Sequence analysis of SSCP bands revealed the existence of wild-type sequence (bands 1 and 3) and mutant sequence (bands 2 and 4). DNA sequencing revealed a 15 base pair deletion, while the affected children (lanes 2 and 3) are homozygous. Haplotype analysis demonstrated homozygosity at the STGD locus in the two affected individuals.

FIGS. 7A–H shows the localization of ABCR transcripts to photoreceptor cells. In situ hybridization was performed with digoxigenin-labeled riboprobes and visualized using an alkaline phosphatase conjugated anti-digoxigenin antibody. FIGS. 7A–D displays hybridization results of retina and choroid from a pigmented mouse (C57/B16); FIGS. 7E and 7F shows hybridization results of retina and choroid from an albino rat; and FIGS. 7G and 7H exhibits hybridization results of retina from a macaque monkey. FIGS. 7A, 7E, and 7G display results from a mouse *abcr* antisense probe; FIG. 7B exhibit results from a mouse *abcr* sense probe; FIG. 7C shows results from a macaque rhodopsin antisense probe; and FIGS. 7D, 7F, and 7H display results from a mouse blue cone pigment antisense probe. ABCR transcripts are localized to the inner segments of the photoreceptor cell layer, a pattern that matches the distribution of rhodopsin transcripts but is distinct from the distribution of cone visual pigment transcripts. Hybridization is not observed in the RPE or choroid, as seen most clearly in the albino rat eye (arrowhead in FIG. 7E). The retinal layers indicated in FIG. 7B are: OS, outer segments; IS, inner segments; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer.

FIG. 8 provides a pGEM®-T Vector map.

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DETAILED DESCRIPTION OF THE
INVENTION

The present invention is directed to the nucleic acid and protein sequences encoding ATP binding cassette transporter. The ATP binding cassette transporter of the present invention is retina specific ATP binding cassette transporter (ABCR); more particularly, ABCR may be isolated from retinal cells, preferably photoreceptor cells. The present invention provides nucleotide sequences of ABCR including genomic sequences, SEQ ID NO: 1, and cDNA sequences SEQ ID NO: 2 and 5. Novel polypeptide sequences, SEQ ID NOS: 3 and 6, for ABCR, are the translated products of SEQ ID NOS: 2 and 5, respectively, and are also included in the present invention.

SEQ ID NO:1 provides the human genomic DNA sequence of ABCR. SEQ ID NOS: 2 and 5 provide wild-type cDNA sequences of human ABCR, which result in translated products SEQ ID NOS: 3 and 6, respectively. While not intending to be bound by any particular theory or theories of operation, it is believed that SEQ ID NOS: 2 and 5 are isoforms of ABCR cDNA. The difference between SEQ ID NOS: 2 and 5 may be accounted for by an additional sequence in SEQ ID NO: 2 which is added between bases 4352 and 4353 of SEQ ID NO: 5. This difference is thought to arise from alternative splicing of the nascent transcript of ABCR, in which an alternative exon 30, SEQ ID NO: 4, is excluded. This alternative exon encodes an additional 38 amino acids, SEQ ID NO: 11.

Nucleic acids within in the scope of the present invention include cDNA, RNA, genomic DNA, fragments or portions within the sequences, antisense oligonucleotides. Sequences encoding the ABCR also include amino acid, polypeptide, and protein sequences. Variations in the nucleic acid and polypeptide sequences of the present invention are within the scope of the present invention and include N terminal and C terminal extensions, transcription and translation modifications, and modifications in the cDNA sequence to facilitate and improve transcription and translation efficiency. In addition, changes within the wild-type sequences identified herein which changed sequence retains substantially the same wild-type activity, such that the changed sequences are substantially similar to the ABCR sequences identified, are also considered within the scope of the present invention. Mismatches, insertions, and deletions which permit substantial similarity to the ABCR sequences, such as similarity in residues in hydrophobicity, hydrophilicity, basicity, and acidity, will be known to those of skill in the art once armed with the present disclosure. In addition, the isolated, or purified, sequences of the present invention may be natural, recombinant, synthetic, or a combination thereof. Wild-type activity associated with the ABCR sequences of the present invention include, inter alia, all or part of a sequence, or a sequence substantially similar thereto, that codes for ATP binding cassette transporter.

The genomic, SEQ ID NO: 1, and cDNA, SEQ ID NOS: 2 and 5, sequences are identified in FIG. 3 and encode ABCR, certain mutations of which are responsible for the class of retinal disorders known as retinal or macular degenerations. Macular degeneration is characterized by macular dystrophy, various alterations of the peripheral retina, central visual impairment, progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, frequent appearance of orange-yellow flecks distributed around the macula and/or the midretinal periphery, and subretinal deposition of lipofuscin-like material. Retinal and macular degenerative diseases include and are not limited to

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Stargardt Disease, Fundus Flavimaculatus, age-related macular degeneration, and may include disorders variously called retinitis pigmentosa, combined rod and cone dystrophies, cone dystrophies and degenerations, pattern dystrophy, bull's eye maculopathies, and various other retinal degenerative disorders, some induced by drugs, toxins, environmental influences, and the like. Stargardt Disease is an autosomal recessive retinal disorder characterized by juvenile to adult-onset macular and retinal dystrophy. Fundus Flavimaculatus often displays later age of onset and slower progression. Some environmental insults and drug toxicities may create similar retinal degenerations. Linkage analysis reveals that Stargardt Disease and Fundus Flavimaculatus may be allelic autosomal recessive disorders with slightly different clinical manifestations. The identification of the ABCR gene suggests that different mutations within ABCR may be responsible for these clinical phenomena.

The present invention is also directed to a method of screening for an agent that modifies ATP binding cassette transporter comprising combining purified ATP binding cassette transporter with an agent suspected of modifying ATP binding cassette transporter and observing a change in at least one characteristic associated with ATP binding cassette transporter.

"Modify" and variations thereof include changes such as and not limited to inhibit, suppress, delay, retard, slow, suspend, obstruct, and restrict, as well as induce, encourage, provoke, and cause. Modify may also be defined as complete inhibition such that macular degeneration is arrested, stopped, or blocked. Modifications may, directly or indirectly, inhibit or substantially inhibit, macular degeneration or induce, or substantially induce, macular degeneration, under certain circumstances.

Methods of identifying an agent that inhibits macular degeneration are embodied by the present invention and comprise combining purified ATP binding cassette transporter from a patient suspected of having macular degeneration and an agent suspected of interacting with the ATP binding cassette transporter and observing an inhibition in at least one of the characteristics of diseases associated with the ATP binding cassette transporter. Accordingly, such methods serve to reduce or prevent macular degeneration, such as in human patients. In addition, the present invention provides for methods of identifying an agent that induces onset of at least one characteristic associated with ATP binding cassette transporter comprising combining purified wild-type ATP binding cassette transporter with an agent suspected of inducing a macular degenerative disease and observing the onset of a characteristic associated with macular degeneration. Thus, such methods provide methods of using laboratory animals to determine causative agents of macular degeneration. The ATP binding cassette transporter may be provided for in the methods identified herein in the form of nucleic acids, such as and not limited to SEQ ID NOS: 1, 2, and 5 or as an amino acid, SEQ ID NOS: 3 and 6, for example. Accordingly, transcription and translation inhibitors may be separately identified. Characteristics associated with macular degeneration include and are not limited to central visual impairment, progressive bilateral atrophy of the macular retinal pigment epithelium (RPE) and neuroepithelium, and the frequent appearance of orange-yellow flecks distributed around the macula and/or the midretinal periphery. Accordingly, observing one or more of the characteristics set forth above results in identification of an agent that induces macular degeneration, whereas reduction or inhibition of at least one of the characteristics results in identification of an agent that inhibits macular degeneration.

Mutational analysis of ABCR in Stargardt Disease families revealed thus far seventy four mutations including fifty four single amino acid substitutions, five nonsense mutations resulting in early truncation of the protein, six frame shift mutations resulting in early truncation of the protein, three in-frame deletions resulting in loss of amino acid residues from the protein, and six splice site mutations resulting in incorrect processing of the nascent RNA transcript, see Table 2. Compound heterozygotes for mutations in ABCR were found in forty two families. Homozygous mutations were identified in three families with consanguineous parentage. Accordingly, mutations in wild-type ABCR which result in activities that are not associated with wild-type ABCR are herein referred to as sequences which are associated with macular degeneration. Such mutations include missense mutations, deletions, insertions, substantial differences in hydrophobicity, hydrophilicity, acidity, and basicity. Characteristics which are associated with retinal or macular degeneration include and are not limited to those characteristics set forth above.

Mutations in wild-type ABCR provide a method of detecting macular degeneration. Retinal or macular degeneration may be detected by obtaining a sample comprising patient nucleic acids from a patient tissue sample; amplifying retina-specific ATP binding cassette receptor specific nucleic acids from the patient nucleic acids to produce a test fragment; obtaining a sample comprising control nucleic acids from a control tissue sample; amplifying control nucleic acids encoding wild-type retina-specific ATP binding cassette receptor to produce a control fragment; comparing the test fragment with the control fragment to detect the presence of a sequence difference in the test fragment, wherein a difference in the test fragment indicates macular degeneration. Mutations in the test fragment, including and not limited to each of the mutations identified above, may provide evidence of macular degeneration.

A purified ABCR protein is also provided by the present invention. The purified ABCR protein may have an amino acid sequence as provided by SEQ ID NOS: 3 and 6.

The present invention is directed to ABCR sequences obtained from mammals from the Order Rodentia, including and not limited to hamsters, rats, and mice; Order Logomorpha, such as rabbits; more particularly the Order Carnivora, including Felines (cats) and Canines (dogs); even more particularly the Order Artiodactyla, Bovines (cows) and Suines (pigs); and the Order Perissodactyla, including Equines (horses); and most particularly the Order Primates, Ceboids and Simioids (monkeys) and Anthropoids (humans and apes). The mammals of most preferred embodiments are humans.

Generally, the sequences of the invention may be produced in host cells transformed with an expression vector comprising a nucleic acid sequence encoding ABCR. The transformed cells are cultured under conditions whereby the nucleic acid sequence coding for ABCR is expressed. After a suitable amount of time for the protein to accumulate, the protein may be purified from the transformed cells.

A gene coding for ABCR may be obtained from a cDNA library. Suitable libraries can be obtained from commercial sources such as Clontech, Palo Alto, Calif. Libraries may also be prepared using the following non-limiting examples: hamster insulin-secreting tumor (HIT), mouse α TC-6, and rat insulinoma (RIN) cells. Positive clones are then subjected to DNA sequencing to determine the presence of a DNA sequence coding for ABCR. DNA sequencing is accomplished using the chain termination method of Sanger et al., *Proc. Nat'l. Acad. Sci., U.S.A.*, 1977, 74, 5463. The

DNA sequence encoding ABCR is then inserted into an expression vector for later expression in a host cell.

Expression vectors and host cells are selected to form an expression system capable of synthesizing ABCR. Vectors including and not limited to baculovirus vectors may be used in the present invention. Host cells suitable for use in the invention include prokaryotic and eukaryotic cells that can be transformed to stably contain and express ABCR. For example, nucleic acids coding for the recombinant protein may be expressed in prokaryotic or eukaryotic host cells, including the most commonly used bacterial host cell for the production of recombinant proteins, *E. coli*. Other microbial strains may also be used, however, such as *Bacillus subtilis*, and other enterobacteriaceae such as *Salmonella typhimurium* or *Serratia marcescens*, various species of *Pseudomonas*, or other bacterial strains.

The preferable eukaryotic system is yeast, such as *Saccharomyces cerevisiae*. Yeast artificial chromosome (YAC) systems are able to accommodate the large size of ABCR gene sequence or genomic clone. The principle of the YAC system is similar to that used in conventional cloning of DNA. Large fragments of cDNA are ligated into two "arms" of a YAC vector, and the ligation mixture is then introduced into the yeast by transformation. Each of the arms of the YAC vector carries a selectable marker as well as appropriately oriented sequences that function as telomeres in yeast. In addition, one of the two arms carries two small fragments that function as a centromere and as an origin of replication (also called an ARS element-autonomously replicating sequences). Yeast transformants that have taken up and stably maintained an artificial chromosome are identified as colonies on agar plates containing the components necessary for selection of one or both YAC arms. YAC vectors are designed to allow rapid identification of transformants that carry inserts of genomic DNA. Insertion of genomic DNA into the cloning site interrupts a suppressor tRNA gene and results in the formation of red rather than white colonies by yeast strains that carry an amber *ade2* gene.

To clone in YAC vectors, genomic DNA from the test organism is prepared under conditions that result in relatively little shearing such that its average size is several million base pairs. The cDNA is then ligated to the arms of the YAC vector, which has been appropriately prepared to prevent self-ligation. As an alternative to partial digestion with *EcoRI*, YAC vectors may be used that will accept genomic DNA that has been digested to completion with rarely cutting restriction enzymes such as *NotI* or *MluI*.

In addition, insect cells, such as *Spodoptera frugiperda*; chicken cells, such as E3C/O and SL-29; mammalian cells, such as HeLa, Chinese hamster ovary cells (CHO), COS-7 or MDCK cells and the like may also be used. The foregoing list is illustrative only and is not intended in any way to limit the types of host cells suitable for expression of the nucleic acid sequences of the invention.

As used herein, expression vectors refer to any type of vector that can be manipulated to contain a nucleic acid sequence coding for ABCR, such as plasmid expression vectors, viral vectors, and yeast expression vectors. The selection of the expression vector is based on compatibility with the desired host cell such that expression of the nucleic acid encoding ABCR results. Plasmid expression vectors comprise a nucleic acid sequence of the invention operably linked with at least one expression control element such as a promoter. In general, plasmid vectors contain replicon and control sequences derived from species compatible with the host cell. To facilitate selection of plasmids containing nucleic acid sequences of the invention, plasmid vectors

may also contain a selectable marker such as a gene coding for antibiotic resistance. Suitable examples include the genes coding for ampicillin, tetracycline, chloramphenicol, or kanamycin resistance.

Suitable expression vectors, promoters, enhancers, and other expression control elements are known in the art and may be found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, second edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989), incorporated herein by reference in its entirety.

Transformed host cells containing a DNA sequence encoding ABCR may then be grown in an appropriate medium for the host. The cells are then grown until product accumulation reaches desired levels at which time the cells are then harvested and the protein product purified in accordance with conventional techniques. Suitable purification methods include, but are not limited to, SDS PAGE electrophoresis, phenylboronate-agarose, reactive green 19-agarose, concanavalin A sepharose, ion exchange chromatography, affinity chromatography, electrophoresis, dialysis and other methods of purification known in the art.

Protein preparations, of purified or unpurified ABCR by host cells, are accordingly produced which comprise ABCR and other material such as host cell components and/or cell medium, depending on the degree of purification of the protein.

The invention also includes a transgenic non-human animal, including and not limited to mammals, such as and not limited to a mouse, rat, or hamster, comprising a sequence encoding ABCR, or fragment thereof that substantially retains ABCR activity, introduced into the animal or an ancestor of the animal. The sequence may be wild-type or mutant and may be introduced into the animal at the embryonic or adult stage. The sequence is incorporated into the genome of an animal such that it is chromosomally incorporated into an activated state. A transgenic non-human animal has germ cells and somatic cells that contain an ABCR sequence. Embryo cells may be transfected with the gene as it occurs naturally, and transgenic animals are selected in which the gene has integrated into the chromosome at a locus which results in activation. Other activation methods include modifying the gene or its control sequences prior to introduction into the embryo. The embryo may be transfected using a vector containing the gene.

In addition, a transgenic non-human animal may be engineered wherein ABCR is suppressed. For purposes of the present invention, suppression of ABCR includes, and is not limited to strategies which cause ABCR not to be expressed. Such strategies may include and are not limited to inhibition of protein synthesis, pre-mRNA processing, or DNA replication. Each of the above strategies may be accomplished by antisense inhibition of ABCR gene expression. Many techniques for transferring antisense sequences into cells are known to those of skill, including and not limited to microinjection, viral-mediated transfer, somatic cell transformation, transgene integration, and the like, as set forth in Pinkert, Carl, *Transgenic Animal Technology*, 1994, Academic Press, Inc., San Diego, Calif., incorporated herein by reference in its entirety.

Further, a transgenic non-human animal may be prepared such that ABCR is knocked out. For purposes of the present invention, a knock-out includes and is not limited to disruption or rendering null the ABCR gene. A knock-out may be accomplished, for example, with antisense sequences for ABCR. The ABCR gene may be knocked out by injection of an antisense sequence for all or part of the ABCR sequence such as an antisense sequence for all or part of SEQ ID NO:

2. Once ABCR has been rendered null, correlation of the ABCR to macular degeneration may be tested. Sequences encoding mutations affecting the ABCR may be inserted to test for alterations in various retinal and macular degenerations exhibited by changes in the characteristics associated with retinal and macular degeneration. ANABCR knock-out may be engineered by inserting synthetic DNA into the animal chromosome by homologous recombination. In this method, sequences flanking the target and insert DNA are identical, allowing strand exchange and crossing over to occur between the target and insert DNA. Sequences to be inserted typically include a gene for a selectable marker, such as drug resistance. Sequences to be targeted are typically coding regions of the genome, in this case part of the ABCR gene. In this process of homologous recombination, targeted sequences are replaced with insert sequences thus disrupting the targeted gene and rendering it nonfunctional. This nonfunctional gene is called a null allele of the gene.

To create the knockout mouse, a DNA construct containing the insert DNA and flanking sequences is made. This DNA construct is transfected into pluripotent embryonic stem cells competent for recombination. The identical flanking sequences align with one another, and chromosomal recombination occurs in which the targeted sequence is replaced with the insert sequence, as described in Bradley, A., *Production and Analysis of Chimeric Mice, in Teratocarcinomas and Embryonic Stem Cells—A Practical Approach*, 1987, E. Roberson, Editor, IRC Press, pages 113–151. The stem cells are injected into an embryo, which is then implanted into a female animal and allowed to be born. The animals may contain germ cells derived from the injected stem cells, and subsequent matings may produce animals heterozygous and homozygous for the disrupted gene.

Transgenic non-human animals may also be useful for testing nucleic acid changes to identify additional mutations responsible for macular degeneration. A transgenic non-human animal may comprise a recombinant ABCR.

The present invention is also directed to gene therapy. For purposes of the present invention, gene therapy refers to the transfer and stable insertion of new genetic information into cells for the therapeutic treatment of diseases or disorders. A foreign sequence or gene is transferred into a cell that proliferates to spread the new sequence or gene throughout the cell population. Sequences include antisense sequence of all or part of ABCR, such as an antisense sequence to all or part of the sequences identified as SEQ ID NO: 1, 2, and 5. Known methods of gene transfer include microinjection, electroporation, liposomes, chromosome transfer, transfection techniques, calcium-precipitation transfection techniques, and the like. In the instant case, macular degeneration may result from a loss of gene function, as a result of a mutation for example, or a gain of gene function, as a result of an extra copy of a gene, such as three copies of a wild-type gene, or a gene over expressed as a result of a mutation in a promoter, for example. Expression may be altered by activating or deactivating regulatory elements, such as a promoter. A mutation may be corrected by replacing the mutated sequence with a wild-type sequence or inserting an antisense sequence to bind to an over expressed sequence or to a regulatory sequence.

Numerous techniques are known in the art for the introduction of foreign genes into cells and may be used to construct the recombinant cells for purposes of gene therapy, in accordance with this embodiment of the invention. The technique used should provide for the stable transfer of the heterologous gene sequence to the stem cell, so that the

heterologous gene sequence is heritable and expressible by stem cell progeny, and so that the necessary development and physiological functions of the recipient cells are not disrupted. Techniques which may be used include but are not limited to chromosome transfer (e.g., cell fusion, chromosome-mediated gene transfer, micro cell-mediated gene transfer), physical methods (e.g., transfection, spheroplast fusion, microinjection, electroporation, liposome carrier), viral vector transfer (e.g., recombinant DNA viruses, recombinant RNA viruses) and the like (described in Cline, M. J., 1985, *Pharmac. Ther.* 29:69-92, incorporated herein by reference in its entirety).

The term "purified", when used to describe the state of nucleic acid sequences of the invention, refers to nucleic acid sequences substantially free of nucleic acid not coding for ABCR or other materials normally associated with nucleic acid in non-recombinant cells, i.e., in its "native state."

The term "purified" or "in purified form" when used to describe the state of an ABCR nucleic acid, protein, polypeptide, or amino acid sequence, refers to sequences substantially free, to at least some degree, of cellular material or other material normally associated with it in its native state. Preferably the sequence has a purity (homogeneity) of at least about 25% to about 100%, More preferably the purity is at least about 50%, when purified in accordance with standard techniques known in the art.

In accordance with methods of the present invention, methods of detecting retinal or macular degenerations in a patient are provided comprising obtaining a patient tissue sample for testing. The tissue sample may be solid or liquid, a body fluid sample such as and not limited to blood, skin, serum, saliva, sputum, mucus, bone marrow, urine, lymph, and a tear; and feces. In addition, a tissue sample from amniotic fluid or chorion may be provided for the detection of retinal or macular degeneration in utero in accordance with the present invention.

A test fragment is defined herein as an amplified sample comprising ABCR-specific nucleic acids from a patient suspected of having retinal or macular degeneration. A control fragment is an amplified sample comprising normal or wild-type ABCR-specific nucleic acids from an individual not suspected of having retinal or macular degeneration.

The method of amplifying nucleic acids may be the polymerase chain reaction using a pair of primers wherein at least one primer within the pair is selected from the group consisting of SEQ ID NOS: 12-113. When the polymerase chain reaction is the amplification method of choice, a pair of primers may be used such that one primer of the pair is selected from the group consisting of SEQ ID NOS: 12-113.

Nucleic acids, such as DNA (such as and not limited to, genomic DNA and cDNA) and/or RNA (such as and not limited to mRNA) are obtained from the patient sample. Preferably RNA is obtained.

Nucleic acid extraction is followed by amplification of the same by any technique known in the art. The amplification step includes the use of at least one primer sequence which is complementary to a portion of ABCR-specific expressed nucleic acids or sequences on flanking intronic genomic sequences in order to amplify exon or coding sequences. Primer sequences useful in the amplification methods include and are not limited to SEQ ID NOS: 12-113, which may be used in the amplification methods. Any primer sequence of about 10 nucleotides to about 35 nucleotides, more preferably about 15 nucleotides to about 30 nucleotides, even more preferably about 17 nucleotides to about 25 nucleotides may be useful in the amplification step of the

methods of the present invention. In addition, mismatches within the sequences identified above, which achieve the methods of the invention, such that the mismatched sequences are substantially complementary and thus hybridizable to the sequence sought to be identified, are also considered within the scope of the disclosure. Mismatches which permit substantial similarity to SEQ ID NOS: 12-113, such as and not limited to sequences with similar hydrophobicity, hydrophilicity, basicity, and acidity, will be known to those of skill in the art once armed with the present disclosure. The primers may also be unmodified or modified. Primers may be prepared by any method known in the art such as by standard phosphoramidite chemistry. See Sambrook et al., *supra*.

The method of amplifying nucleic acids may be the polymerase chain reaction using a pair of primers wherein at least one primer within the pair is selected from the group consisting of SEQ ID NOS: 12-113. When the polymerase chain reaction is the amplification method of choice, a pair of primers may be used such that one primer of the pair is selected from the group consisting of SEQ ID NOS: 12-113.

When an amplification method includes the use of two primers, a first primer and a second primer, such as in the polymerase chain reaction, one of the first primer or second primer may be selected from the group consisting of SEQ ID NOS: 12-113. Any primer pairs which copy and amplify nucleic acids between the pairs pointed toward each other and which are specific for ABCR may be used in accordance with the methods of the present invention.

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR) which is described in detail in U.S. Pat. Nos. 4,683,195, 4,683,202 and 4,800,159, and in Innis et al., *PCR Protocols*, Academic Press, Inc., San Diego Calif., 1990, each of which is incorporated herein by reference in its entirety. Briefly, in PCR, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase (e.g., Taq polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction products and the process is repeated. Alternatively, a reverse transcriptase PCR amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in EPA No.320,308, incorporated herein by reference in its entirety. In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Pat. No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Application No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA which has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence which can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[alpha-thio]triphosphates in one strand of a restriction site (Walker, G. T., et al., *Proc. Natl. Acad. Sci. (U.S.A.)* 1992, 89:392-396, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, i.e. nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and which involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

ABCR-specific nucleic acids can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-ABCR specific DNA and middle sequence of ABCR specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe identified as distinctive products, generate a signal which is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a ABCR-specific expressed nucleic acid.

Still other amplification methods described in GB Application No. 2 202 328, and in PCT Application No. PCT/US89/01025, each of which is incorporated by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes are added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh D., et al., *Proc. Natl. Acad. Sci. (U.S.A.)* 1989, 86:1173, Gingeras T. R., et al., PCT Application WO 88/10315, each of which is incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a clinical sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer which has ABCR-specific sequences. Following polymerization, DNA/RNA hybrids are digested with RNase H while double

stranded DNA molecules are heat denatured again. In either case the single stranded DNA is made fully double stranded by addition of second ABCR-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into double stranded DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate ABCR-specific sequences.

Davey, C., et al., European Patent Application Publication No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA ("dsDNA") which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA: RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

Miller, H. I., et al., PCT application WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; i.e. new templates are not produced from the resultant RNA transcripts. Other amplification methods include "race" disclosed by Frohman, M. A., In: *PCR Protocols: A Guide to Methods and Applications* 1990, Academic Press, N.Y.) and "one-sided PCR" (Ohara, O., et al., *Proc. Natl. Acad. Sci. (U.S.A.)* 1989, 86:5673-5677), all references herein incorporated by reference in their entirety.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu, D. Y. et al., *Genomics* 1989, 4:560, incorporated herein by reference in its entirety), may also be used in the amplification step of the present invention.

Test fragment and control fragment may be amplified by any amplification methods known to those of skill in the art, including and not limited to the amplification methods set forth above. For purposes of the present invention, amplification of sequences encoding patient and wild-type ABCR includes amplification of a portion of a sequence such as and not limited to a portion of an ABCR sequence of SEQ ID NO: 1, such as sequence of a length of about 10 nucleotides to about 1,000 nucleotides, more preferably about 10 nucleotides to about 100 nucleotides, or having at least 10

nucleotides occurring anywhere within the SEQ ID NO: 1, where sequence differences are known to occur within ABCR test fragments. Thus, for example, a portion of the sequence encoding ABCR of a patient sample and a control sample may be amplified to detect sequence differences between these two sequences.

Following amplification of the test fragment and control fragment, comparison between the amplification products of the test fragment and control fragment is carried out. Sequence changes such as and not limited to nucleic acid transition, transversion, and restriction digest pattern alterations may be detected by comparison of the test fragment with the control fragment.

Alternatively, the presence or absence of the amplification product may be detected. The nucleic acids are fragmented into varying sizes of discrete fragments. For example, DNA fragments may be separated according to molecular weight by methods such as and not limited to electrophoresis through an agarose gel matrix. The gels are then analyzed by Southern hybridization. Briefly, DNA in the gel is transferred to a hybridization substrate or matrix such as and not limited to a nitrocellulose sheet and a nylon membrane. A labeled probe encoding an ABCR mutation is applied to the matrix under selected hybridization conditions so as to hybridize with complementary DNA localized on the matrix. The probe may be of a length capable of forming a stable duplex. The probe may have a size range of about 200 to about 10,000 nucleotides in length, preferably about 500 nucleotides in length, and more preferably about 2,454 nucleotides in length. Mismatches which permit substantial similarity to the probe, such as and not limited to sequences with similar hydrophobicity, hydrophilicity, basicity, and acidity, will be known to those of skill in the art once armed with the present disclosure. Various labels for visualization or detection are known to those of skill in the art, such as and not limited to fluorescent staining, ethidium bromide staining for example, avidin/biotin, radioactive labeling such as ³²P labeling, and the like. Preferably, the product, such as the PCR product, may be run on an agarose gel and visualized using a stain such as ethidium bromide. See Sambrook et al., supra. The matrix may then be analyzed by autoradiography to locate particular fragments which hybridize to the probe. Yet another alternative is the sequencing of the test fragment and the control fragment to identify sequence differences. Methods of nucleic acid sequencing are known to those of skill in the art, including and not limited to the methods of Maxam and Gilbert, *Proc. Natl. Acad. Sci., USA* 1977, 74, 560–564 and Sanger, *Proc. Natl. Acad. Sci., USA* 1977, 74, 5463–5467.

A pharmaceutical composition comprising all or part of a sequence for ABCR may be delivered to a patient suspected of having retinal or macular degeneration. The sequence may be an antisense sequence. The composition of the present invention may be administered alone or may generally be administered in admixture with a pharmaceutical carrier. The pharmaceutically-acceptable carrier may be selected with regard to the intended route of administration and the standard pharmaceutical practice. The dosage will be about that of the sequence alone and will be set with regard to weight, and clinical condition of the patient. The proportional ratio of active ingredient to carrier will naturally depend, inter alia, on the chemical nature, solubility, and stability of the sequence, as well as the dosage contemplated.

The sequences of the invention may be employed in the method of the invention singly or in combination with other compounds, including and not limited to other sequences set

forth in the present invention. The method of the invention may also be used in conjunction with other treatments such as and not limited to antibodies, for example. For in vivo applications the amount to be administered will also depend on such factors as the age, weight, and clinical condition of the patient. The composition of the present invention may be administered by any suitable route, including as an eye drop, inoculation and injection, for example, intravenous, intraocular, oral, intraperitoneal, intramuscular, subcutaneous, topically, and by absorption through epithelial or mucocutaneous linings, for example, conjunctival, nasal, oral, vaginal, rectal and gastrointestinal.

The mode of administration of the composition may determine the sites in the organism to which the compound will be delivered. For instance, topical application may be administered in creams, ointments, gels, oils, emulsions, pastes, lotions, and the like. For parenteral administration, the composition may be used in the form of sterile aqueous or non-aqueous solution which may contain another solute, for example, sufficient salts, glucose or dextrose to make the solution isotonic. A non-aqueous solution may be comprise an oil, for example. For oral mode of administration, the present invention may be used in the form of tablets, capsules, lozenges, troches, powders, syrups, elixirs, aqueous solutions and suspension, and the like. Various disintegrants, such as starch, and lubricating agents may be used. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, certain sweetening and/or flavoring agents may be added.

A diagnostic kit for detecting retinal or macular degeneration comprising in one or more containers at least one primer which is complementary to an ABCR sequence and a means for visualizing amplified DNA is also within the scope of the present invention. Alternatively, the kit may comprise two primers. In either case, the primers may be selected from the group consisting of SEQ ID NOS: 12–113, for example. The diagnostic kit may comprise a pair of primers wherein one primer within said pair is complementary to a region of the ABCR gene, wherein one of said pair of primers is selected from the group consisting of SEQ ID NO: 12–113, a probe specific to the amplified product, and a means for visualizing amplified DNA, and optionally including one or more size markers, and positive and negative controls. The diagnostic kit of the present invention may comprise one or more of a fluorescent dye such as ethidium bromide stain, ³²p, and biotin, as a means for visualizing or detecting amplified DNA. Optionally the kit may include one or more size markers, positive and negative controls, restriction enzymes, and/or a probe specific to the amplified product.

The following examples are illustrative but are not meant to be limiting of the invention.

EXAMPLES

Identification of the ABCR as a Candidate Gene for STGD

One of the 21 new human genes from the ABC superfamily, hereafter called ABCR (retina-specific ABC transporter), was identified (Allikmets et al. 1996) among expressed sequence tags (ESTs) obtained from 5,000 human retina cDNA clones (Wang, Y., Macke, J. P., Abella, B. S., Andreasson, K., Worley, P., Gilbert, D. J., Copeland, N. G., Jenkins, N. A., and Nathans, J. (1996)) and among ESTs obtained from human retina cDNA clones by the I.M.A.G.E. consortium (Lennon et al., 1996). ABCR is closely related to

the previously described mouse and human ABC1 and ABC2 genes (Luciani et al., 1994; Allikmets et al., 1995). To determine whether ABCR might cause a disease, the gene was mapped with a whole genome radiation hybrid panel (GeneBridge 4; Research Genetics, Huntsville, Ala.). ABCR mapped to the human chromosome 1p13-p21 region, close to microsatellite markers D1S236 and D1S188. To define further the location of the gene, PCR primers, 3'UTR-For 5'ATCCTCTGACTCAGCAATCACA, SEQ ID NO: 7, and 3'UTR-Rev 5'TTGCAATTACAAATGCAATGG, SEQ ID NO: 8, from the putative 3' untranslated region were used to screen YACs from the previously described contig between these anonymous markers (Anderson et al., 1995). At least 12 YACs contain the 3' end of the ABCR gene, including 924_e_9, 759_d_7, 775_c_2, 782_b_4, 982_g_5, 775_b_2, 765_a_3, 751_f_2, 848_e_3, 943_h_8, 934_g_7, and 944_b_12 (FIG. 1). These YACs delineate a region containing the STGD gene between markers D1S3361 and D1S236 (Anderson et al., 1995).

Expression of the ABCR Gene

Additional support suggesting that ABCR is a candidate STGD gene came from expression studies and inspection of the EST databases.

Searches of the dbEST (Boguski et al., 1993) database were performed with BLAST on the NCBI file server (Altschul et al., 1990). Amino acid alignments were generated with PILEUP (Feng and Doolittle, 1987). Sequences were analyzed with programs of the Genetics Computer Group package (Devereaux et al., 1984) on a VAX computer.

Clones corresponding to the mouse ortholog of the human ABCR gene were isolated from the mouse retina cDNA library and end-sequenced. The chromosomal location of the mouse ABCR gene was determined on The Jackson Laboratory (Bar Harbor, Me.) interspecific backcross mapping panel (C57BL/6J*Ei*×SPRET/*Ei*)F1×SPRET/*Ei* (Rowe et al., 1994) known as Jackson BSS. Mapping was performed by SSCP analysis with the primers MABCR1F 5'ATC CAT ACC CTT CCC ACT CC, SEQ ID NO: 9, and MABCR1R 5' GCA GCA GAA GAT AAG CAC ACC, SEQ ID NO: 10. The allele pattern of the *Abcr* was compared to the 250 other loci mapped previously in the Jackson BSS cross (<http://www.jax.org>).

DNA fragments used as probes were purified on a 1% low-melting temperature agarose gel. The probe sequences are set forth within the genomic sequence of SEQ ID NO: 1 and FIG. 3. DNA was labeled directly in agarose with the Random Primed DNA Labeling Kit (Boehringer Mannheim, Indianapolis, Ind.) and hybridized to multiple tissue Northern blot and a Master blot (Clontech, Palo Alto, Calif.), according to the manufacturer's instructions. Each blot contained 2 µg of poly A⁺ RNA from various human tissues. Total RNA was isolated from adult rat tissues using the guanidinium thiocyanate method (Chomczynski and Saachi, 1987) and resolved by agarose gel electrophoresis in the presence of formaldehyde (Sambrook et al., 1989). Hybridization with the mouse ABCR probe was performed in 50% formamide, 5×SSC at 42° C., and filters were washed in 0.1×SSC at 68° C.

Hybridization of a 3' ABCR cDNA probe to a multiple tissue Northern blot and a MasterBlot (Clontech, Palo Alto, Calif.) indicated that the gene was not expressed detectably in any of the 50 non-retinal fetal and adult tissues examined, consistent with the observation that all 12 of the ABCR clones in the EST database originated from retinal cDNA libraries. Furthermore, screening cDNA libraries from both developing mouse eye and adult human retina with ABCR

probes revealed an estimated at 0.1%–1% frequency of ABCR clones of all cDNA clones in the library. Hybridization of the ABCR probe to a Northern blot containing total RNA from rat retina and other tissues showed that the expression of this gene is uniquely retina-specific (FIG. 2). The transcript size is estimated to be 8 kb.

Sequence and Exon/Intron Structure of the ABCR cDNA

Several ESTs that were derived from retina cDNA libraries and had high similarity to the mouse *Abc1* gene were used to facilitate the assembly of most of the ABCR cDNA sequence. Retina cDNA clones were linked by RT-PCR, and repetitive screening of a human retina cDNA library with 3' and 5' PCR probes together with 5' RACE were used to characterize the terminal sequences of the gene.

cDNA clones containing ABCR sequences were obtained from a human retina cDNA library (Nathans et al., 1986) and sequenced fully. Primers were designed from the sequences of cDNA clones from 5' and 3' regions of the gene and used to link the identified cDNA clones by RT-PCR with retina QUICK-Clone cDNA (Clontech, Palo Alto, Calif.) as a template. PCR products were cloned into pGEM®-T vector (Promega, Madison, Wis.). Mouse ABCR cDNA clones were obtained from screening a developing mouse eye cDNA library (H. Sun, A. Lanahan, and J. Nathans, unpublished). The pGEM®-T Vector is prepared by cutting pGEM®-5Zf(+) DNA with EcoR V and adding to a 3' terminal thymidine to both ends. These single 3'-T overhangs at the insertion site greatly improve the efficiency of ligation of PCR products because of the nontemplate-dependent addition of a single deoxyadenosine (A) to the 3'-ends of PCR products by many thermostable polymerases. The pGEM®-5Zf(+) Vector contains the origin of replication of the filamentous phage f1 and can be used to produce ssDNA. The plasmid also contains T7 and SP6 RNA polymerase promoters flanking a multiple cloning region within the α-peptide coding region for the enzyme β-galactosidase. Insertional inactivation of the α-peptide allows recombinant clones to be identified directly by color screening on indicator plates. cDNA clones from various regions of the ABCR gene were used as probes to screen a human genomic library in Lambda FIX II (#946203, Stratagene, LaJolla, Calif.). Overlapping phage clones were mapped by EcoRI and BamHI digestion. A total of 6.9 kb of the ABCR sequence was assembled, (FIG. 3) resulting in a 6540 bp (2180 amino acid) open reading frame.

Screening of a bacteriophage lambda human genomic library with cDNA probes yielded a contig that spans approximately 100 kb and contains the majority of the ABCR coding region. The exon/intron structure of all fifty one exons of the gene were characterized by direct sequencing of genomic and cDNA clones. Intron sizes were estimated from the sizes of PCR products using primers from adjacent exons with genomic phage clones as templates.

Primers for the cDNA sequences of the ABCR were designed with the PRIMER program (Lincoln et al., 1991). Both ABCR cDNA clones and genomic clones became templates for sequencing. Sequencing was performed with the Taq Dyedeoxy Terminator Cycle Sequencing kit (Applied Biosystems, Foster City, Calif.), according to the manufacturer's instructions. Sequencing reactions were resolved on an ABI 373A automated sequencer. Positions of introns were determined by comparison between genomic and cDNA sequences. Primers for amplification of individual exons were designed from adjacent intron sequences 20–50 bp from the splice site and are set forth in Table 1.

TABLE 1

Exon/intron Primers for ABCR		
PRIMER	SEQUENCE	SEQ ID NO
ABCR.EXON1:F	ACCCTCTGCTAAGCTCAGAG	12
ABCR.EXON1:R	ACCCACACTTCCAACCTG	13
ABCR.EXON2:F	AAGTCTACTGCACACATGG	14
ABCR.EXON2:R	ACACTCCCACCCCAAGATC	15
ABCR.EXON3:F	TTCCAAAAAGGCCAATC	16
ABCR.EXON3:R	CACGCACGTGTGCATTGAG	17
ABCR.EXON4:F	GCTATTTCCCTTATTAATGAGGC	18
ABCR.EXON4:R	CCAACTCTCCCTGTTCTTTC	19
ABCR.EXON5:F	TGTTTCCAATCGACTCTGGC	20
ABCR.EXON5:R	TTCTTGCCTTTCTCAGGCTGG	21
ABCR.EXON6:F	GTATTCCCAGGTTCTGTGG	22
ABCR.EXON6:R	TACCCAGGAATCACCTTG	23
ABCR.EXON7:F	AGCATATAGGAGATCAGACTG	24
ABCR.EXON7:R	TGACATAAGTGGGGTAAATGG	25
ABCR.EXON8:F	GAGCATTTGGCCTCACAGCAG	26
ABCR.EXON8:R	CCCCAGGTTTGTTCACC	27
ABCR.EXON9:F	AGACATGTGATGTGGATACAC	28
ABCR.EXON9:R	GTGGGAGGTCCAGGGTACAC	29
ABCR.EXON10:F	AGGGGCAGAAAAGACACAC	30
ABCR.EXON10:R	TAGCGATTAACCTTTTCCTGG	31
ABCR.EXON11:F	CTCTTCAGGGAGCCTTAGC	32
ABCR.EXON11:R	TTCAAGACCACTTGACTTGC	33
ABCR.EXON12:F	TGGGACAGCAGCCTTATC	34
ABCR.EXON12:R	CCAAATGTAATTTCCCACTGAC	35
ABCR.EXON13:F	AATGAGTTCCGAGTCACCCTG	36
ABCR.EXON13:R	CCCATTCCGGTGTGATGG	37
ABCR.EXON14:F	TCCATCTGGGCTTTGTTCTC	38
ABCR.EXON14:R	AATCCAGGCACATGAACAGG	39
ABCR.EXON15:F	AGGCTGGTGGGAGAGAGC	40
ABCR.EXON15:R	AGTGGACCCCTCAGAGG	41
ABCR.EXON16:F	CTGTTGCATTGGATAAAAGGC	42
ABCR.EXON16:R	GATGAATGGAGAGGGCTGG	43
ABCR.EXON17:F	CTGCGGTAAGGTAGGATAGGG	44
ABCR.EXON17:R	CACACCGTTTACATAGAGGGC	45
ABCR.EXON18:F	CCTCTCCCTCCTTTCTCTG	46
ABCR.EXON18:R	GTCAGTTTCCGTAGGCTTC	47
ABCR.EXON19:F	TGGGGCCATGTAATTAGGC	48

TABLE 1-continued

Exon/intron Primers for ABCR		
PRIMER	SEQUENCE	SEQ ID NO
ABCR.EXON19:R	TGGGAAAGAGTAGACAGCCG	49
ABCR.EXON20:F	ACTGAACCTGGTGTGGGG	50
ABCR.EXON20:R	TATCTCTGCCTGTGCCAG	51
ABCR.EXON21:F	GTAAGATCAGCTGCTGGAAG	52
ABCR.EXON21:R	GAAGCTCTCCTGCACCAAGC	53
ABCR.EXON22:F	AGGTACCCCAATGCC	54
ABCR.EXON22:R	TCATTGTGGTTCCAGTACTCAG	55
ABCR.EXON23:F	TTTTTGCAACTATATAGCCAGG	56
ABCR.EXON23:R	AGCCTGTGTGAGTAGCCATG	57
ABCR.EXON24:F	GCATCAGGGCGAGGCTGTC	58
ABCR.EXON24:R	CCCAGCAATACTGGGAGATG	59
ABCR.EXON25:F	GGTAACCTCACAGTCTTCC	60
ABCR.EXON25:R	GGGAACGATGGCTTTTTC	61
ABCR.EXON26:F	TCCCATTATGAAGCAATACC	62
ABCR.EXON26:R	CCTTAGACTTTTCGAGATGG	63
ABCR.EXON27:F	GCTACCAGCCTGGTATTTTCATTG	64
ABCR.EXON27:R	GTTATAACCCATGCCTGAAG	65
ABCR.EXON28:F	TGCACGCGCACGTGTGAC	66
ABCR.EXON28:R	TGAAGGTCCCAGTGAAGTGGG	67
ABCR.EXON29:F	CAGCAGCTATCCAGTAAAGG	68
ABCR.EXON29:R	AACGCCTGCCATCTTGAAC	69
ABCR.EXON30:F	GTTGGGCACAATTCTTATGC	70
ABCR.EXON30:R	GTTGTTTGGAGGTCAGGTAC	71
ABCR.EXON31:F	AACATCACCCAGCTGTTCCAG	72
ABCR.EXON31:R	ACTCAGGAGATACCAGGGAC	73
ABCR.EXON32:F	GGAAGACAACAAGCAGTTTCAC	74
ABCR.EXON32:R	ATCTACTGCCCTGATCATAAC	75
ABCR.EXON33:F	AAGACTGAGACTTCAGTCTTC	76
ABCR.EXON33:R	GGTGTGCCTTTTAAAAGTGTGC	77
ABCR.EXON34:F	TTCATGTTTCCCTACAAAACCC	78
ABCR.EXON34:R	CATGAGAGTTTCTCATTCATGG	79
ABCR.EXON35:F	TGTTTACATGGTTTTTAGGGCC	80
ABCR.EXON35:R	TTCAGCAGGAGGAGGGATG	81
ABCR.EXON36:F	CCTTTCTTCACTGATTTCTGC	82
ABCR.EXON36:R	AATCAGCACTTCGCGGTG	83
ABCR.EXON37:F	TGTAAGGCCTTCCCAAAGC	84
ABCR.EXON37:R	TGGTCCTTCAGCGCACACAC	85

TABLE 1-continued

Exon/intron Primers for ABCR		
PRIMER	SEQUENCE	SEQ ID NO
ABCR.EXON38:F	CATTTTGCAGAGCTGGCAGC	86
ABCR.EXON38:R	CTTCTGTCAGGAGATGATCC	87
ABCR.EXON39:F	GGAGTGCATTATATCCAGACG	88
ABCR.EXON39:R	CCTGGCTCTGCTTGACCAAC	89
ABCR.EXON40:F	TGCTGTCTGTGAGAGCATC	90
ABCR.EXON40:R	GTAACCCTCCCAGCTTTGG	91
ABCR.EXON41:F	CAGTTCACACATAAGGCCTG	92
ABCR.EXON41:R	CAGTTCTGGATGCCCTGAG	93
ABCR.EXON42:F	GAAGAGAGGTCCCATGGAAAGG	94
ABCR.EXON42:R	GCTTGACATAAGCATATCAATTG	95
ABCR.EXON43:F	CTCCTAAACCATCCTTTGCTC	96
ABCR.EXON43:R	AGGCAGGCACAAGAGCTG	97
ABCR.EXON44:F	CTTACCCTGGGGCCTGAC	98
ABCR.EXON44:R	CTCAGAGCCACCCTACTATAG	99
ABCR.EXON45:F	GAAGCTTCTCCAGCCCTAGC	100
ABCR.EXON45:R	TGCACTCTCATGAAACAGGC	101
ABCR.EXON46:F	GTTTGGGGTGTGTTGCTTGTC	102
ABCR.EXON46:R	ACCTCTTTCCCCAACCAGAG	103
ABCR.EXON47:F	GAAGCAGTAATCAGAAGGGC	104
ABCR.EXON47:R	GCCTCACATTCTTCCATGCTG	105
ABCR.EXON48:F	TCACATCCCACAGGCAAGAG	106
ABCR.EXON48:R	TTCCAAGTGTCATGGAGAAC	107
ABCR.EXON49:F	ATTACCTTAGGCCCAACCAC	108
ABCR.EXON49:R	ACACTGGGTGTTCTGGACC	109
ABCR.EXON50:F	GTGTAGGGTGGTGTGTTTCC	110
ABCR.EXON50:R	AAGCCAGTGAACCAGCTGG	111
ABCR.EXON51:F	TCAGCTGAGTGCCCTTCAG	112
ABCR.EXON51:R	AGGTGAGCAAGTCAGTTTCGG	113

In Table 1, "F" indicates forward, i.e., 5' to 3', "R" indicates reverse, i.e., 3' to 5'. PCR conditions were 95° C. for 8 minutes; 5 cycles at 62° C. for 20 seconds, 72° C. for 30 seconds; 35 cycles at 60° C. for 20 seconds, 72° C. for 30 seconds; 72° C. for 5 minutes (except that^a was performed at 94° C. for 5 minutes); 5 cycles at 94° C. for 40 seconds; 60° C. for 30 seconds; 72° C. for 20 seconds; 35 cycles at 94° C. for 40 seconds; 56° C. for 30 seconds; 72° C. for 20 seconds, and 72° C. for 5 minutes.

Amplification of exons was performed with AmpliTaq Gold polymerase in a 25 µl volume in 1xPCR buffer supplied by the manufacturer (Perkin Elmer, Foster City, Calif.). Samples were heated to 95° C. for 10 minutes and amplified for 35–40 cycles at 96° C. for 20 seconds; 58° C. for 30 seconds; and 72° C. for 30 seconds. PCR products

were analyzed on 1–1.5% agarose gels and in some cases digested with an appropriate restriction enzymes to verify their sequence. Primer sequences and specific reaction conditions are set forth in Table 1. The sequence of the ABCR cDNA has been deposited with GenBank under accession # U88667.

Homology to ABC Superfamily Members

A BLAST search revealed that ABCR is most closely related to the previously characterized mouse *Abc1* and *Abc2* genes (Luciani et al., 1994) and to another human gene (ABCC) which maps to chromosome 16p13.3 (Klugbauer and Hofmann, 1996). These genes, together with ABCR and a gene from *C. elegans* (GenBank #Z29117), form a subfamily of genes specific to multicellular organisms and not represented in yeast (Michaelis and Berkower, 1995; Allikmets et al., 1996). Alignment of the CDNA sequence of ABCR with the *Abc1*, *Abc2*, and ABCC genes revealed, as expected, the highest degree of homology within the ATP-binding cassettes. The predicted amino acid identity of the ABCR gene to mouse *Abc1* was 70% within the ATP-binding domains; even within hydrophobic membrane-spanning segments, homology ranged between 55 and 85% (FIG. 4). The putative ABCR initiator methionine shown in FIGS. 3 and 4 corresponds to a methionine codon at the 5' end of *Abc1* (Luciani et al., 1994).

ABCR shows the composition of a typical full-length ABC transporter that consists of two transmembrane domains (TM), each with six membrane spanning hydrophobic segments, as predicted by a hydropathy plot (data not shown), and two highly conserved ATP-binding domains (FIGS. 3 and 4). In addition, the HH1 hydrophobic domain, located between the first ATP and second TM domain and specific to this subfamily (Luciani et al., 1994), showed a predicted 57% amino acid identity (24 of 42 amino acids) with the mouse *Abc1* gene.

To characterize the mouse ortholog of ABCR, cDNA clones from a developing mouse eye library were isolated. A partial sequence of the mouse cDNA was utilized to design PCR primers to map the mouse *Abcr* gene in an interspecific backcross mapping panel (Jackson BSS). The allele pattern of *Abcr* was compared to 2450 other loci mapped previously in the Jackson BSS cross; linkage was found to the distal end of chromosome 3 (FIG. 5). No recombinants were observed between *Abcr* and D13Mit13. This region of the mouse genome is syntenic with human chromosome 1p13-p21. Thus far, no eye disease phenotype has been mapped to this region of mouse chromosome 3.

Compound Heterozygous and Homozygous Mutations in STGD Patients

One hundred forty-five North American and three Saudi Arabian families with STGD/FFM were examined. Among these, at least four were consanguineous families in which the parents were first cousins. Entry criteria for the characterization of the clinical and angiographic diagnosis of Stargardt disease, ascertainment of the families, and methodology for their collection, including the consanguineous families from Saudi Arabia, were as provided in Anderson et al., 1995; and Anderson, 1996.

Mutational analysis of the ABCR gene was pursued in the above identified one hundred forty-eight STGD families previously ascertained by strict definitional criteria and shown to be linked to chromosome 1p (Anderson et al., 1995; Anderson, 1996). To date, all 51 exons have been used for mutation analysis.

Mutations were detected by a combined SSCP (Orita et al., 1989) and heteroduplex analysis (White et al., 1992)

under optimized conditions (Glavč and Dean, 1993). Genomic DNA samples (50 ng) were amplified with Ampli-Taq Gold polymerase in 1×PCR buffer supplied by the manufacturer (Perkin Elmer, Foster City, Calif.) containing [α - 32 P] dCTP. Samples were heated to 95° C. for 10 minutes and amplified for 35–40 cycles at 96° C. for 20 seconds; 58° C. for 30 seconds; and 72° C. for 30 seconds. Products were diluted in 1:3 stop solution, denatured at 95° C. for 5 minutes, chilled in ice for 5 minutes, and loaded on gels. Gel formulations include 6% acrylamide:Bis (2.6% cross-linking), 10% glycerol at room temperature, 12 W; and 10% acrylamide:Bis (1.5% cross-linking), at 4° C., 70 W. Gels were run for 2–16 hours (3000 Vh/100 bp), dried, and exposed to X-ray film for 2–12 hours. Some exons were analyzed by SSCP with MDE acrylamide (FMC Bioproducts, Rockland, Me.) with and without 10% glycerol for 18 hours, 4 watts at room temperature with α -P 32 -dCTP labeled DNA. Heteroduplexes were identified from the double-stranded DNA at the bottom of the gels, and SSCPs were identified from the single-stranded region. Samples showing variation were compared with other family members to assess segregation of the alleles and with at least 40 unrelated control samples, from either Caucasian or Saudi Arabian populations, to distinguish mutations from polymorphisms unrelated to STGD. PCR products with SSCP or heteroduplex variants were obtained in a 25 μ l volume, separated on a 1% agarose gel, and isolated by a DNA purification kit (PGC Scientific, Frederick, Md.). Sequencing was performed on an ABI sequencer with both dye primer and dye terminator chemistry.

Some mutations were identified with a heteroduplex analysis protocol (Roa et al., 1993). Equimolar amounts of control and patient PCR products were mixed in 0.2 ml tubes. Two volumes of PCR product from a normal individual served as a negative control, and MPZ exon 3 from patient BAB731 as a positive control (Roa et al., 1996). Samples were denatured at 95° C. for 2 minutes and cooled to 35° C. at a rate of 1° C./minute. Samples were loaded onto 1.0 mm thick, 40 cm MDE gels (FMC Bioproducts, Rockland, Me.), electrophoresed at 600–800 V for 15–20 hours, and visualized with ethidium bromide. Samples showing a variant band were reamplified with biotinylated forward and reverse primers and immobilized on streptavidin-conjugated beads (Warner et al. 1996). The resulting single strands were sequenced by the dideoxy-sequencing method with Sequenase 2.0 (Amersham, Arlington Heights, Ill.).

A total of seventy five mutations were identified, the majority representing missense mutations in conserved amino acid positions. However, several insertions and deletions representing frameshifts were also found (Table 2). Two missense alterations (D847H, R943Q) were found in at least one control individual, suggesting that they are neutral polymorphisms. The remaining mutations were found in patients having macular degeneration and were not found in at least 220 unrelated normal controls (440 chromosomes), consistent with the interpretation that these alterations represent disease-causing mutations, not polymorphisms. One of the mutations, 5892+1 G→T, occurs in family AR144 in which one of the affected children is recombinant for the flanking marker D1S236 (Anderson et al., 1995). This mutation, however, is present in the father as well as in both affected children. Therefore, the ABCR gene is non-recombinant with respect to the Stargardt disease locus.

The mutations are scattered throughout the coding sequence of the ABCR gene (see Table 2 and FIGS. 3A–H), although clustering within the conserved regions of the ATP-binding domains is noticeable. Homozygous mutations

were detected in three likely consanguineous families, two Saudi Arabian and one North American (Anderson et al., 1995), in each of which only the affected individuals inherited the identical disease allele (Table 2; FIG. 6). Forty two compound heterozygous families were identified in which the two disease alleles were transmitted from different parents to only the affected offspring (Table 2).

TABLE 2

Mutations in the ABCR gene in STGD Families				
Nucleotide	Amino Acid	#Families	Exon	
0223T->G	C75G	1		3
0634C->T	R212C	1	6	
0664del13	fs	1		6
0746A->G	D249G	1	6	
1018T->G	Y340D	2	8	
1411G->A	E471K	1	11	
1569T->G	D523E	1	12	
1715G->A	R572Q	2	12	
1715G->C	R572P	1	12	
1804C->T	R602W	1		13
1822T->A	F608I	1		13
1917C->A	Y639X	1	13	
2453G->A	G818E	1	16	
2461T->A	W821R	1		16
2536G->C	D846H	1	16	
2588G->C	G863A	11	17	
2791G->A	V931M	1		19
2827C->T	R943W	1		19
2884delC	fs	1		19
2894A->G	N965S	3	19	
3083C->T	A1028V	14		21
3211delGT	fs	1		22
3212C->T	S1071L	1		22
3215T->C	V1072A	1		22
3259G->A	E1087K	1		22
3322C->T	R1108C	6		22
3364G->A	E1122K	1		23
3385G->T	R1129C	1		23
3386G->T	R1129L	1		23
3602T->G	L1201R	1		24
3610G->A	D1204N	1		25
4139C->T	P1380L	2		28
4195G->A	E1399K	1		28
4222T->C	W1408R	3		28
4232insTATG	fs	1		28
4253+5G->T	splice	1		28
4297G->A	V1433I	1		29
4316G->A	G1439D	1		29
4319T->C	F1440S	1		29
4346G->A	W1449X	1		29
4462T->C	C1488R	1		30
4469G->A	C1490Y	1		31
4577C->T	T1526M	6		32
4594G->A	D1532N	2		32
4947delC	fs	1		36
5041del15	VVAIC1681del	1		37
5196+2T->C	splice	1	37	
5281del9	PAL1761del	1		38
5459G->C	R1820P	1		39
5512C->T	H1838Y	1		40
5527C->T	R1843W	1		40
5585+1G->A	splice	1	41	
5657G->A	G1886E	1		41
5693G->A	R1898H	4		41
5714+5G->A	splice	8	41	
5882G->A	G1961E	16		43
5898+1G->A	splice	3	43	
5908C->T	L1970F	1		44
5929G->A	G1977S	1		44
6005+1G->T	splice	1	44	
6079C->T	L2027F	11		45
6088C->T	R2030X	1		45
6089G->A	R2030Q	1		45
6112C->T	R2038W	1		45
6148G->C	V2050L	2		46
6166A->T	K2056X	1		46

TABLE 2-continued

Mutations in the ABCR gene in STGD Families			
Nucleotide	Amino Acid	#Families	Exon
6229C->T	R2077W	1	46
6286G->A	E2096K	1	47
6316C->T	R2106C	1	47
6391G->A	E2131K	1	48
6415C->T	R2139W	1	48
6445C->T	R2149X	1	48
6543del36	1181del12	1	49
6709delG	fs	1	49

Mutations are named according to standard nomenclature. The column headed "Exon" denotes which of the 51 exons of ABCR contain the mutation. The column headed "# Families" denotes the number of Stargardt families which displayed the mutation. The column headed "Nucleotide" gives the base number starting from the A in the initiator ATG, followed by the wild type sequence and an arrow indicating the base it is changed to; del indicates a deletion of selected bases at the given position in the ABCR gene; ins indicates an insertion of selected bases at the given position; splice donor site mutations are indicated by the number of the last base of the given exon, followed by a plus sign and the number of bases into the intron where the mutation occurs. The column headed "Amino Acid" denotes the amino acid change a given mutation causes; fs indicates a frameshift mutation leading to a truncated protein; splice indicates a splice donor site mutation; del indicates an in-frame deletion of the given amino acids.

Mutations are named according to standard nomenclature. Exon numbering according to the nucleotide position starting from the A in the initiator ATG.

In Situ Hybridization

STGD is characterized histologically by a massive accumulation of a lipofuscin-like substance in the retinal pigment epithelium (RPE). This characteristic has led to the suggestion that STGD represents an RPE storage disorder (Blacharski et al., 1988). It was therefore of interest that ABCR transcripts were found to be abundant in the retina. To identify the site(s) of ABCR gene expression at higher resolution and to determine whether the gene is also expressed in the RPE, the distribution of ABCR transcripts was visualized by in situ hybridization to mouse, rat, bovine, and macaque ocular tissues.

In situ hybridization with digoxigenin-labeled riboprobes was performed as described by Schaeren-Wiemers and Gerfin-Moser, 1993. For mouse and rat, unfixed whole eyes were frozen and sectioned; macaque retinas were obtained following cardiac perfusion with paraformaldehyde as described (Zhou et al., 1996). An extra incubation of 30 min in 1% Triton X-100, 1xPBS was applied to the fixed monkey retina sections immediately after the acetylation step. The templates for probe synthesis were: (1) a 1.6 kb fragment encompassing the 3' end of the mouse *Abcr* coding region, (2) a full length cDNA clone encoding the mouse blue cone pigment (Chiu et al., 1994), and (3) a macaque rhodopsin coding region segment encoding residues 133 to 254 (Nickells, R. W., Burgoyne, C. F., Quigley, H. A., and Zack, D. J. (1995)).

This analysis showed that ABCR transcripts are present exclusively within photoreceptor cells (FIG. 7). ABCR transcripts are localized principally to the rod inner segments, a distribution that closely matches that of rhodopsin

gene transcripts. Interestingly, ABCR hybridization was not observed at detectable levels in cone photoreceptors, as judged by comparisons with the hybridization patterns obtained with a blue cone pigment probe (compare FIG. 7A and FIG. 7D, FIG. 7E with FIG. 7F and FIG. 7G with FIG. 7H). Because melanin granules might obscure a weak hybridization signal in the RPE of a pigmented animal, the distribution of ABCR transcripts was also examined in both albino rats and albino mice. In these experiments, the ABCR hybridization signal was seen in the photoreceptor inner segments and was unequivocally absent from the RPE (FIG. 7E). Given that ABCR transcripts in each of these mammals, including a primate, are photoreceptor-specific, it is highly likely that the distribution of ABCR transcripts conforms to this pattern as well in the human retina.

The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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Gly Met Leu Pro Trp Leu Gln Gly Ile Phe Cys Asn Val Asn Asn Pro
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Tyr Asn Asn Ser Ile Leu Ala Arg Val Tyr Arg Asp Phe Gln Glu Leu
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Leu Met Asn Ala Pro Glu Ser Gln His Leu Gly Arg Ile Trp Thr Glu
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Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
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Arg Ile Ala Gly Arg Gly Ile Arg Ile Arg Asp Ile Leu Lys Asp Glu
 145 150 155 160

Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
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Val Val Tyr Leu Leu Ile Asn Ser Gln Val Arg Pro Glu Gln Phe Ala
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His Gly Val Pro Asp Leu Ala Leu Lys Asp Ile Ala Cys Ser Glu Ala
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Glu Asp Thr Leu Tyr Ala Asn Val Asp Phe Phe Lys Leu Phe Arg Val
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Trp Gly Gly Ile Leu Ser Asp Met Ser Pro Arg Ile Gln Glu Phe Ile
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Gln Asn Gly Gly Pro Glu Thr Phe Thr Lys Leu Met Gly Ile Leu Ser
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Ser Thr Arg Lys Asp Pro Ile Tyr Ser Tyr Asp Arg Arg Thr Thr Ser
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Ser	Ser	Leu	Pro	Pro	His	Val	Lys	Tyr	Lys	Ile	Arg	Met	Asp	Ile	Asp
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Arg Ile Met Asn Val Ser Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys
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Glu Ile Pro Asp Phe Leu Lys His Leu Glu Thr Glu Asp Asn Ile Lys
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Val Ala His Asn Ala Ile Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser
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Pro Glu Glu Tyr Gly Ile Thr Val Ile Ser Gln Pro Leu Asn Leu Thr
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Lys Glu Gln Leu Ser Glu Ile Thr Val Leu Thr Thr Ser Val Asp Ala
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Val Val Ala Ile Cys Val Ile Phe Ser Met Ser Phe Val Pro Ala Ser
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Phe Val Leu Tyr Leu Ile Gln Glu Arg Val Asn Lys Ser Lys His Leu
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Gln Phe Ile Ser Gly Val Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe
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Pro	Ala	Leu	Val	Ala	Leu	Leu	Leu	Leu	Tyr	Gly	Trp	Ala	Val	Ile	Pro	1765	1770	1775	
Met	Met	Tyr	Pro	Ala	Ser	Phe	Leu	Phe	Asp	Val	Pro	Ser	Thr	Ala	Tyr	1780	1785	1790	
Val	Ala	Leu	Ser	Cys	Ala	Asn	Leu	Phe	Ile	Gly	Ile	Asn	Ser	Ser	Ala	1795	1800	1805	
Ile	Thr	Phe	Ile	Leu	Glu	Leu	Phe	Asp	Asn	Asn	Arg	Thr	Leu	Leu	Arg	1810	1815	1820	
Phe	Asn	Ala	Val	Leu	Arg	Lys	Leu	Leu	Ile	Val	Phe	Pro	His	Phe	Cys	1825	1830	1835	1840
Leu	Gly	Arg	Gly	Leu	Ile	Asp	Leu	Ala	Leu	Ser	Gln	Ala	Val	Thr	Asp	1845	1850	1855	
Val	Tyr	Ala	Arg	Phe	Gly	Glu	Glu	His	Ser	Ala	Asn	Pro	Phe	His	Trp	1860	1865	1870	
Asp	Leu	Ile	Gly	Lys	Asn	Leu	Phe	Ala	Met	Val	Val	Glu	Gly	Val	Val	1875	1880	1885	
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Trp	Ile	Ala	Glu	Pro	Thr	Lys	Glu	Pro	Ile	Val	Asp	Glu	Asp	Asp	Asp	1905	1910	1915	1920
Val	Ala	Glu	Glu	Arg	Gln	Arg	Ile	Ile	Thr	Gly	Gly	Asn	Lys	Thr	Asp	1925	1930	1935	
Ile	Leu	Arg	Leu	His	Glu	Leu	Thr	Lys	Ile	Tyr	Leu	Gly	Thr	Ser	Ser	1940	1945	1950	
Pro	Ala	Val	Asp	Arg	Leu	Cys	Val	Gly	Val	Arg	Pro	Gly	Glu	Cys	Phe	1955	1960	1965	
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Thr	Ala	Ile	Ala	Leu	Ile	Gly	Cys	Pro	Pro	Leu	Val	Leu	Leu	Asp	Glu	2085	2090	2095	
Pro	Thr	Thr	Gly	Met	Asp	Pro	Gln	Ala	Arg	Arg	Met	Leu	Trp	Asn	Val	2100	2105	2110	
Ile	Val	Ser	Ile	Ile	Arg	Lys	Gly	Arg	Ala	Val	Val	Leu	Thr	Ser	His	2115	2120	2125	
Ser	Met	Glu	Glu	Cys	Glu	Ala	Leu	Cys	Thr	Arg	Leu	Ala	Ile	Met	Val	2130	2135	2140	
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Asp Leu Leu Pro Asp Leu Asn Pro Val Glu Gln Phe Phe Gln Gly Asn	2180	2185	2190
Phe Pro Gly Ser Val Gln Arg Glu Arg His Tyr Asn Met Leu Gln Phe	2195	2200	2205
Gln Val Ser Ser Ser Ser Leu Ala Arg Ile Phe Gln Leu Leu Leu Ser	2210	2215	2220
His Lys Asp Ser Leu Leu Ile Glu Glu Tyr Ser Val Thr Gln Thr Thr	2225	2230	2235
Leu Asp Gln Val Phe Val Asn Phe Ala Lys Gln Gln Thr Glu Ser His	2245	2250	2255
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Asp

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<210> SEQ ID NO 6

<211> LENGTH: 2235

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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Leu His Ile Leu Ser Gln Phe Met Asp Thr Leu Arg Thr His Pro Glu
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Glu Thr Leu Thr Leu Phe Leu Ile Lys Asn Ile Gly Leu Ser Asp Ser
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545					550					555					560
Ser	Ser	Leu	Pro	Pro	His	Val	Lys	Tyr	Lys	Ile	Arg	Met	Asp	Ile	Asp
				565					570					575	
Val	Val	Glu	Lys	Thr	Asn	Lys	Ile	Lys	Asp	Arg	Tyr	Trp	Asp	Ser	Gly
			580					585					590		
Pro	Arg	Ala	Asp	Pro	Val	Glu	Asp	Phe	Arg	Tyr	Ile	Trp	Gly	Gly	Phe
		595					600						605		
Ala	Tyr	Leu	Gln	Asp	Met	Val	Glu	Gln	Gly	Ile	Thr	Arg	Ser	Gln	Val
	610					615					620				
Gln	Ala	Glu	Ala	Pro	Val	Gly	Ile	Tyr	Leu	Gln	Gln	Met	Pro	Tyr	Pro

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625	630	635	640
Cys Phe Val Asp Asp Ser Phe Met Ile Ile Leu Asn Arg Cys Phe Pro 645 650 655			
Ile Phe Met Val Leu Ala Trp Ile Tyr Ser Val Ser Met Thr Val Lys 660 665 670			
Ser Ile Val Leu Glu Lys Glu Leu Arg Leu Lys Glu Thr Leu Lys Asn 675 680 685			
Gln Gly Val Ser Asn Ala Val Ile Trp Cys Thr Trp Phe Leu Asp Ser 690 695 700			
Phe Ser Ile Met Ser Met Ser Ile Phe Leu Leu Thr Ile Phe Ile Met 705 710 715 720			
His Gly Arg Ile Leu His Tyr Ser Asp Pro Phe Ile Leu Phe Leu Phe 725 730 735			
Leu Leu Ala Phe Ser Thr Ala Thr Ile Met Leu Cys Phe Leu Leu Ser 740 745 750			
Thr Phe Phe Ser Lys Ala Ser Leu Ala Ala Ala Cys Ser Gly Val Ile 755 760 765			
Tyr Phe Thr Leu Tyr Leu Pro His Ile Leu Cys Phe Ala Trp Gln Asp 770 775 780			
Arg Met Thr Ala Glu Leu Lys Lys Ala Val Ser Leu Leu Ser Pro Val 785 790 795 800			
Ala Phe Gly Phe Gly Thr Glu Tyr Leu Val Arg Phe Glu Glu Gln Gly 805 810 815			
Leu Gly Leu Gln Trp Ser Asn Ile Gly Asn Ser Pro Thr Glu Gly Asp 820 825 830			
Glu Phe Ser Phe Leu Leu Ser Met Gln Met Met Leu Leu Asp Ala Ala 835 840 845			
Cys Tyr Gly Leu Leu Ala Trp Tyr Leu Asp Gln Val Phe Pro Gly Asp 850 855 860			
Tyr Gly Thr Pro Leu Pro Trp Tyr Phe Leu Leu Gln Glu Ser Tyr Trp 865 870 875 880			
Leu Ser Gly Glu Gly Cys Ser Thr Arg Glu Glu Arg Ala Leu Glu Lys 885 890 895			
Thr Glu Pro Leu Thr Glu Glu Thr Glu Asp Pro Glu His Pro Glu Gly 900 905 910			
Ile His Asp Ser Phe Phe Glu Arg Glu His Pro Gly Trp Val Pro Gly 915 920 925			
Val Cys Val Lys Asn Leu Val Lys Ile Phe Glu Pro Cys Gly Arg Pro 930 935 940			
Ala Val Asp Arg Leu Asn Ile Thr Phe Tyr Glu Asn Gln Ile Thr Ala 945 950 955 960			
Phe Leu Gly His Asn Gly Ala Gly Lys Thr Thr Thr Leu Ser Ile Leu 965 970 975			
Thr Gly Leu Leu Pro Pro Thr Ser Gly Thr Val Leu Val Gly Gly Arg 980 985 990			
Asp Ile Glu Thr Ser Leu Asp Ala Val Arg Gln Ser Leu Gly Met Cys 995 1000 1005			
Pro Gln His Asn Ile Leu Phe His His Leu Thr Val Ala Glu His Met 1010 1015 1020			
Leu Phe Tyr Ala Gln Leu Lys Gly Lys Ser Gln Glu Glu Ala Gln Leu 1025 1030 1035 1040			
Glu Met Glu Ala Met Leu Glu Asp Thr Gly Leu His His Lys Arg Asn 1045 1050 1055			

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Glu Glu Ala Gln Asp Leu Ser Gly Gly Met Gln Arg Lys Leu Ser Val
 1060 1065 1070

Ala Ile Ala Phe Val Gly Asp Ala Lys Val Val Ile Leu Asp Glu Pro
 1075 1080 1085

Thr Ser Gly Val Asp Pro Tyr Ser Arg Arg Ser Ile Trp Asp Leu Leu
 1090 1095 1100

Leu Lys Tyr Arg Ser Gly Arg Thr Ile Ile Met Pro Thr His His Met
 1105 1110 1115 1120

Asp Glu Ala Asp His Gln Gly Asp Arg Ile Ala Ile Ile Ala Gln Gly
 1125 1130 1135

Arg Leu Tyr Cys Ser Gly Thr Pro Leu Phe Leu Lys Asn Cys Phe Gly
 1140 1145 1150

Thr Gly Leu Tyr Leu Thr Leu Val Arg Lys Met Lys Asn Ile Gln Ser
 1155 1160 1165

Gln Arg Lys Gly Ser Glu Gly Thr Cys Ser Cys Ser Ser Lys Gly Phe
 1170 1175 1180

Ser Thr Thr Cys Pro Ala His Val Asp Asp Leu Thr Pro Glu Gln Val
 1185 1190 1195 1200

Leu Asp Gly Asp Val Asn Glu Leu Met Asp Val Val Leu His His Val
 1205 1210 1215

Pro Glu Ala Lys Leu Val Glu Cys Ile Gly Gln Glu Leu Ile Phe Leu
 1220 1225 1230

Leu Pro Asn Lys Asn Phe Lys His Arg Ala Tyr Ala Ser Leu Phe Arg
 1235 1240 1245

Glu Leu Glu Glu Thr Leu Ala Asp Leu Gly Leu Ser Ser Phe Gly Ile
 1250 1255 1260

Ser Asp Thr Pro Leu Glu Glu Ile Phe Leu Lys Val Thr Glu Asp Ser
 1265 1270 1275 1280

Asp Ser Gly Pro Leu Phe Ala Gly Gly Ala Gln Gln Lys Arg Glu Asn
 1285 1290 1295

Val Asn Pro Arg His Pro Cys Leu Gly Pro Arg Glu Lys Ala Gly Gln
 1300 1305 1310

Thr Pro Gln Asp Ser Asn Val Cys Ser Pro Gly Ala Pro Ala Ala His
 1315 1320 1325

Pro Glu Gly Gln Pro Pro Pro Glu Pro Glu Cys Pro Gly Pro Gln Leu
 1330 1335 1340

Asn Thr Gly Thr Gln Leu Val Leu Gln His Val Gln Ala Leu Leu Val
 1345 1350 1355 1360

Lys Arg Phe Gln His Thr Ile Arg Ser His Lys Asp Phe Leu Ala Gln
 1365 1370 1375

Ile Val Leu Pro Ala Thr Phe Val Phe Leu Ala Leu Met Leu Ser Ile
 1380 1385 1390

Val Ile Leu Pro Phe Gly Glu Tyr Pro Ala Leu Thr Leu His Pro Trp
 1395 1400 1405

Ile Tyr Gly Gln Gln Tyr Thr Phe Phe Ser Met Asp Glu Pro Gly Ser
 1410 1415 1420

Glu Gln Phe Thr Val Leu Ala Asp Val Leu Leu Asn Lys Pro Gly Phe
 1425 1430 1435 1440

Gly Asn Arg Cys Leu Lys Glu Gly Trp Leu Pro Cys Ser Thr Arg Glu
 1445 1450 1455

Lys Leu Thr Met Leu Pro Glu Cys Pro Glu Gly Ala Gly Gly Leu Pro
 1460 1465 1470

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Pro Pro Gln Arg Thr Gln Arg Ser Thr Glu Ile Leu Gln Asp Leu Thr
 1475 1480 1485

Asp Arg Asn Ile Ser Asp Phe Leu Val Lys Thr Tyr Pro Ala Leu Ile
 1490 1495 1500

Arg Ser Ser Leu Lys Ser Lys Phe Trp Val Asn Glu Gln Arg Tyr Gly
 1505 1510 1515 1520

Gly Ile Ser Ile Gly Gly Lys Leu Pro Val Val Pro Ile Thr Gly Glu
 1525 1530 1535

Ala Leu Val Gly Phe Leu Ser Asp Leu Gly Arg Ile Met Asn Val Ser
 1540 1545 1550

Gly Gly Pro Ile Thr Arg Glu Ala Ser Lys Glu Ile Pro Asp Phe Leu
 1555 1560 1565

Lys His Leu Glu Thr Glu Asp Asn Ile Lys Val Trp Phe Asn Asn Lys
 1570 1575 1580

Gly Trp His Ala Leu Val Ser Phe Leu Asn Val Ala His Asn Ala Ile
 1585 1590 1595 1600

Leu Arg Ala Ser Leu Pro Lys Asp Arg Ser Pro Glu Glu Tyr Gly Ile
 1605 1610 1615

Thr Val Ile Ser Gln Pro Leu Asn Leu Thr Lys Glu Gln Leu Ser Glu
 1620 1625 1630

Ile Thr Val Leu Thr Thr Ser Val Asp Ala Val Val Ala Ile Cys Val
 1635 1640 1645

Ile Phe Ser Met Ser Phe Val Pro Ala Ser Phe Val Leu Tyr Leu Ile
 1650 1655 1660

Gln Glu Arg Val Asn Lys Ser Lys His Leu Gln Phe Ile Ser Gly Val
 1665 1670 1675 1680

Ser Pro Thr Thr Tyr Trp Val Thr Asn Phe Leu Trp Asp Ile Met Asn
 1685 1690 1695

Tyr Ser Val Ser Ala Gly Leu Val Val Gly Ile Phe Ile Gly Phe Gln
 1700 1705 1710

Lys Lys Ala Tyr Thr Ser Pro Glu Asn Leu Pro Ala Leu Val Ala Leu
 1715 1720 1725

Leu Leu Leu Tyr Gly Trp Ala Val Ile Pro Met Met Tyr Pro Ala Ser
 1730 1735 1740

Phe Leu Phe Asp Val Pro Ser Thr Ala Tyr Val Ala Leu Ser Cys Ala
 1745 1750 1755 1760

Asn Leu Phe Ile Gly Ile Asn Ser Ser Ala Ile Thr Phe Ile Leu Glu
 1765 1770 1775

Leu Phe Asp Asn Asn Arg Thr Leu Leu Arg Phe Asn Ala Val Leu Arg
 1780 1785 1790

Lys Leu Leu Ile Val Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile
 1795 1800 1805

Asp Leu Ala Leu Ser Gln Ala Val Thr Asp Val Tyr Ala Arg Phe Gly
 1810 1815 1820

Glu Glu His Ser Ala Asn Pro Phe His Trp Asp Leu Ile Gly Lys Asn
 1825 1830 1835 1840

Leu Phe Ala Met Val Val Glu Gly Val Val Tyr Phe Leu Leu Thr Leu
 1845 1850 1855

Leu Val Gln Arg His Phe Phe Leu Ser Gln Trp Ile Ala Glu Pro Thr
 1860 1865 1870

Lys Glu Pro Ile Val Asp Glu Asp Asp Asp Val Ala Glu Glu Arg Gln
 1875 1880 1885

Arg Ile Ile Thr Gly Gly Asn Lys Thr Asp Ile Leu Arg Leu His Glu

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1890	1895	1900
Leu Thr Lys Ile Tyr	Leu Gly Thr Ser Ser	Pro Ala Val Asp Arg Leu
1905	1910	1915 1920
Cys Val Gly Val Arg	Pro Gly Glu Cys Phe	Gly Leu Leu Gly Val Asn
	1925	1930 1935
Gly Ala Gly Lys Thr	Thr Thr Phe Lys Met	Leu Thr Gly Asp Thr Thr
	1940	1945 1950
Val Thr Ser Gly Asp	Ala Thr Val Ala Gly	Lys Ser Ile Leu Thr Asn
	1955	1960 1965
Ile Ser Glu Val His	Gln Asn Met Gly Tyr	Cys Pro Gln Phe Asp Ala
	1970	1975 1980
Ile Asp Glu Leu Leu	Thr Gly Arg Glu His	Leu Tyr Leu Tyr Ala Arg
	1985	1990 1995 2000
Leu Arg Gly Val Pro	Ala Glu Glu Ile Glu	Lys Val Ala Asn Trp Ser
	2005	2010 2015
Ile Lys Ser Leu Gly	Leu Thr Val Tyr Ala	Asp Cys Leu Ala Gly Thr
	2020	2025 2030
Tyr Ser Gly Gly Asn	Lys Arg Lys Leu Ser	Thr Ala Ile Ala Leu Ile
	2035	2040 2045
Gly Cys Pro Pro Leu	Val Leu Leu Asp Glu	Pro Thr Thr Gly Met Asp
	2050	2055 2060
Pro Gln Ala Arg Arg	Met Leu Trp Asn Val	Ile Val Ser Ile Ile Arg
	2065	2070 2075 2080
Lys Gly Arg Ala Val	Val Leu Thr Ser His	Ser Met Glu Glu Cys Glu
	2085	2090 2095
Ala Leu Cys Thr Arg	Leu Ala Ile Met Val	Lys Gly Ala Phe Arg Cys
	2100	2105 2110
Met Gly Thr Ile Gln	His Leu Lys Ser Lys	Phe Gly Asp Gly Tyr Ile
	2115	2120 2125
Val Thr Met Lys Ile	Lys Ser Pro Lys Asp	Asp Leu Leu Pro Asp Leu
	2130	2135 2140
Asn Pro Val Glu Gln	Phe Phe Gln Gly Asn	Phe Pro Gly Ser Val Gln
	2145	2150 2155 2160
Arg Glu Arg His Tyr	Asn Met Leu Gln Phe	Gln Val Ser Ser Ser Ser
	2165	2170 2175
Leu Ala Arg Ile Phe	Gln Leu Leu Leu Ser	His Lys Asp Ser Leu Leu
	2180	2185 2190
Ile Glu Glu Tyr Ser	Val Thr Gln Thr Thr	Leu Asp Gln Val Phe Val
	2195	2200 2205
Asn Phe Ala Lys Gln	Gln Thr Glu Ser His	Asp Leu Pro Leu His Pro
	2210	2215 2220
Arg Ala Ala Gly Ala	Ser Arg Gln Ala Gln	Asp
	2225	2230 2235

<210> SEQ ID NO 7

<211> LENGTH: 22

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 7

atcctctgac tcagcaatca ca

22

<210> SEQ ID NO 8

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<211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 8

 ttgcaattac aaatgcaatg g 21

<210> SEQ ID NO 9
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 9

 atccataccc ttcccactcc 20

<210> SEQ ID NO 10
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 10

 gcagcagaag ataagcacac c 21

<210> SEQ ID NO 11
 <211> LENGTH: 38
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

 <400> SEQUENCE: 11

 Glu Tyr Pro Cys Gly Asn Ser Thr Pro Trp Lys Thr Pro Ser Val Ser
 1 5 10 15
 Pro Asn Ile Thr Gln Leu Phe Gln Lys Gln Lys Trp Thr Gln Val Asn
 20 25 30
 Pro Ser Pro Ser Cys Arg
 35

<210> SEQ ID NO 12
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 12

 accctctgct aagctcagag 20

<210> SEQ ID NO 13
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 13

 accccacact tccaacctg 19

<210> SEQ ID NO 14
 <211> LENGTH: 20
 <212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 14

 aagtcctact gcacacatgg 20

<210> SEQ ID NO 15
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 15

 acaactcccac cccaagatc 19

<210> SEQ ID NO 16
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 16

 ttcccaaaaa ggccaactc 19

<210> SEQ ID NO 17
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 17

 cacgcacgtg tgcattcag 19

<210> SEQ ID NO 18
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 18

 gctatttcct tattaatgag gc 22

<210> SEQ ID NO 19
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 19

 ccaactctcc ctggtcttc 20

<210> SEQ ID NO 20
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 20

 tgtttccaat cgactctggc 20

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<210> SEQ ID NO 21
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 21

 ttcttgccctt tctcaggctg g 21

<210> SEQ ID NO 22
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 22

 gtattcccag gttctgtgg 19

<210> SEQ ID NO 23
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 23

 taccacagga atcaccttg 19

<210> SEQ ID NO 24
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 24

 agcatatagg agatcagact g 21

<210> SEQ ID NO 25
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 25

 tgacataagt ggggtaaagt g 21

<210> SEQ ID NO 26
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 26

 gagcattggc ctcacagcag 20

<210> SEQ ID NO 27
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 27

ccccagggtt gtttcacc 18

<210> SEQ ID NO 28
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 28

agacatgtga tgtgatata c 21

<210> SEQ ID NO 29
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 29

gtgggaggtc cagggtacac 20

<210> SEQ ID NO 30
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 30

aggggcagaa aagacacac 19

<210> SEQ ID NO 31
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 31

tagcgattaa ctctttcctg g 21

<210> SEQ ID NO 32
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 32

ctcttcaggg agccttagc 19

<210> SEQ ID NO 33
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 33

ttcaagacca cttgacttgc 20

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<210> SEQ ID NO 34
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 34

 tgggacagca gccttatc 18

<210> SEQ ID NO 35
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 35

 ccaaagttaa tttcccactg ac 22

<210> SEQ ID NO 36
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 36

 aatgagttcc gagtcaccct g 21

<210> SEQ ID NO 37
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 37

 cccattcgcg tgtcatgg 18

<210> SEQ ID NO 38
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 38

 tccatctggg ctttggtctc 20

<210> SEQ ID NO 39
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 39

 aatccaggca catgaacagg 20

<210> SEQ ID NO 40
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

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<400> SEQUENCE: 40
aggctggtgg gagagagc 18

<210> SEQ ID NO 41
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 41
agtggacccc ctgagagg 18

<210> SEQ ID NO 42
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 42
ctggtgcatt ggataaaagg c 21

<210> SEQ ID NO 43
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 43
gatgaatgga gagggctgg 19

<210> SEQ ID NO 44
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 44
ctgcbgtaag gtaggatagg g 21

<210> SEQ ID NO 45
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 45
cacaccgttt acatagagg c 21

<210> SEQ ID NO 46
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 46
cctctcccct cctttcctg 19

<210> SEQ ID NO 47
<211> LENGTH: 19

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<212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 47

 gtcagtttcc gtaggcttc 19

<210> SEQ ID NO 48
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 48

 tggggccatg taattagc 19

<210> SEQ ID NO 49
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 49

 tgggaaagag tagacagccg 20

<210> SEQ ID NO 50
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 50

 actgaacctg gtgtgggg 18

<210> SEQ ID NO 51
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 51

 tatctctgcc tgtgcccg 19

<210> SEQ ID NO 52
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 52

 gtaagatcag ctgctggaag 20

<210> SEQ ID NO 53
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 53

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gaagctctcc tgcaccaagc 20

<210> SEQ ID NO 54
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 54

aggtaccccc acaatgcc 18

<210> SEQ ID NO 55
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 55

tcattgtggt tccagtactc ag 22

<210> SEQ ID NO 56
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 56

tttttgcaac tatatagcca gg 22

<210> SEQ ID NO 57
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 57

agcctgtgtg agtagccatg 20

<210> SEQ ID NO 58
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 58

gcatcagggc gaggctgtc 19

<210> SEQ ID NO 59
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 59

cccagcaata ctgggagatg 20

<210> SEQ ID NO 60
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<220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 60

 ggtaacctca cagtcttcc 19

 <210> SEQ ID NO 61
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 61

 gggaacgatg gctttttgc 19

 <210> SEQ ID NO 62
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 62

 tcccattatg aagcaatacc 20

 <210> SEQ ID NO 63
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 63

 ccttagactt tcgagatgg 19

 <210> SEQ ID NO 64
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 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 64

 gctaccagcc tggatttca ttg 23

 <210> SEQ ID NO 65
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 <212> TYPE: DNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 65

 gttataaccc atgcctgaag 20

 <210> SEQ ID NO 66
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 66

 tgcacgcgca cgtgtgac 18

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<210> SEQ ID NO 67
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 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 67

 tgaaggtccc agtgaagtgg g 21

<210> SEQ ID NO 68
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 68

 cagcagctat ccagtaaagg 20

<210> SEQ ID NO 69
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 69

 aacgcctgcc atcttgaac 19

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 70

 gttgggcaca attcctatgc 20

<210> SEQ ID NO 71
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 gttgtttggg ggtcaggtac 20

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 72

 aacatcaccc agctgttcca g 21

<210> SEQ ID NO 73
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 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

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<400> SEQUENCE: 73
actcaggaga taccaggac 20

<210> SEQ ID NO 74
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 74
ggaagacaac aagcagtttc ac 22

<210> SEQ ID NO 75
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 75
atctactgcc ctgatcatac 20

<210> SEQ ID NO 76
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 76
aagactgaga cttcagtctt c 21

<210> SEQ ID NO 77
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 77
ggtgtgcctt ttaaaagtgt gc 22

<210> SEQ ID NO 78
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 78
ttcatgtttc cctacaaaac cc 22

<210> SEQ ID NO 79
<211> LENGTH: 22
<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

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catgagagtt tctcattcat gg 22

<210> SEQ ID NO 80

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<211> LENGTH: 22
 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 80

 tgtttacatg gtttttaggg cc 22

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 81

 ttcagcagga ggagggatg 19

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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 82

 cctttccttc actgatttct gc 22

<210> SEQ ID NO 83
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 83

 aatcagcact tcgcggtg 18

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 84

 tgtaaggcct tcccaaagc 19

<210> SEQ ID NO 85
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 <212> TYPE: DNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 85

 tggtccttca gcgcacacac 20

<210> SEQ ID NO 86
 <211> LENGTH: 20
 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 86

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cattttgcag agctggcagc 20

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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer
 <400> SEQUENCE: 87

cttctgtcag gagatgatcc 20

<210> SEQ ID NO 88
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer
 <400> SEQUENCE: 88

ggagtgcatt atatccagac g 21

<210> SEQ ID NO 89
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer
 <400> SEQUENCE: 89

cctggctctg cttgaccaac 20

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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer
 <400> SEQUENCE: 90

tgctgtcctg tgagagcatc 20

<210> SEQ ID NO 91
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer
 <400> SEQUENCE: 91

gtaaccctcc cagctttgg 19

<210> SEQ ID NO 92
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer
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cagttcccac ataaggcctg 20

<210> SEQ ID NO 93
 <211> LENGTH: 19
 <212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

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 cagttctgga tgcctgag 19

<210> SEQ ID NO 94
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 94

 gaagagaggt cccatggaaa gg 22

<210> SEQ ID NO 95
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 <212> TYPE: DNA
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 <400> SEQUENCE: 95

 gcttgcataa gcatatcaat tg 22

<210> SEQ ID NO 96
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 <400> SEQUENCE: 96

 ctcctaaacc atcctttgct c 21

<210> SEQ ID NO 97
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 <212> TYPE: DNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 97

 aggcaggcac aagagctg 18

<210> SEQ ID NO 98
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 <212> TYPE: DNA
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 <400> SEQUENCE: 98

 cttaccctgg ggcctgac 18

<210> SEQ ID NO 99
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 <212> TYPE: DNA
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 <400> SEQUENCE: 99

 ctcagagcca ccctactata g 21

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<210> SEQ ID NO 100
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 <212> TYPE: DNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 100

 gaagcttctc cagccctagc 20

<210> SEQ ID NO 101
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 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 101

 tgcactctca tgaacaggc 20

<210> SEQ ID NO 102
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 <212> TYPE: DNA
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 102

 gtttggggtg tttgcttgtc 20

<210> SEQ ID NO 103
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 103

 acctctttcc ccaaccaga g 21

<210> SEQ ID NO 104
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 104

 gaagcagtaa tcagaagggc 20

<210> SEQ ID NO 105
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 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 105

 gcctcacatt cttccatgct g 21

<210> SEQ ID NO 106
 <211> LENGTH: 20
 <212> TYPE: DNA
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 <220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 106

tcacatccca caggcaagag 20

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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 107

ttccaagtgt caatggagaa c 21

<210> SEQ ID NO 108
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 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 108

attaccttag gcccaaccac 20

<210> SEQ ID NO 109
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 109

acactgggtg ttctggacc 19

<210> SEQ ID NO 110
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 110

gtgtagggtg gtgttttcc 19

<210> SEQ ID NO 111
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 <212> TYPE: DNA
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 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 111

aagcccagtg aaccagctgg 20

<210> SEQ ID NO 112
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

<400> SEQUENCE: 112

tcagctgagt gcccttcag 19

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<210> SEQ ID NO 113
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 113

 aggtgagcaa gtcagtttcg g 21

<210> SEQ ID NO 114
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 114

 ggtcttcgtg tgtggtcatt 20

<210> SEQ ID NO 115
 <211> LENGTH: 18
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 115

 ggtccagttc ttccagag 18

<210> SEQ ID NO 116
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 116

 atcctctgac tcagcaatca ca 22

<210> SEQ ID NO 117
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Primer

 <400> SEQUENCE: 117

 ttgcaattac aaatgcaatg g 21

<210> SEQ ID NO 118
 <211> LENGTH: 2261
 <212> TYPE: PRT
 <213> ORGANISM: Murine sp.
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (4)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (175)
 <223> OTHER INFORMATION: Variable amino acid

 <400> SEQUENCE: 118

 Met Ala Cys Xaa Pro Gln Leu Arg Leu Leu Trp Lys Asn Leu Thr
 1 5 10 15
 Phe Arg Arg Arg Gln Thr Cys Gln Leu Leu Leu Glu Val Ala Trp Pro

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20				25				30							
Leu	Phe	Ile	Phe	Leu	Ile	Leu	Ile	Ser	Val	Arg	Leu	Ser	Tyr	Pro	Pro
		35					40						45		
Tyr	Glu	Gln	His	Glu	Cys	His	Phe	Pro	Asn	Lys	Ala	Met	Pro	Ser	Ala
	50					55					60				
Gly	Thr	Leu	Pro	Trp	Val	Gln	Gly	Ile	Ile	Cys	Asn	Ala	Asn	Asn	Pro
	65				70					75					80
Cys	Phe	Arg	Tyr	Pro	Thr	Pro	Gly	Glu	Ala	Pro	Gly	Val	Val	Gly	Asn
				85					90						95
Phe	Asn	Lys	Ser	Ile	Val	Ser	Arg	Leu	Phe	Ser	Asp	Ala	Gln	Arg	Leu
			100					105					110		
Leu	Leu	Tyr	Ser	Gln	Arg	Asp	Thr	Ser	Ile	Lys	Asp	Met	His	Lys	Val
		115					120					125			
Leu	Arg	Met	Leu	Arg	Gln	Ile	Lys	His	Pro	Asn	Ser	Asn	Leu	Lys	Leu
	130					135					140				
Gln	Asp	Phe	Leu	Val	Asp	Asn	Glu	Thr	Phe	Ser	Gly	Phe	Leu	Gln	His
	145				150					155					160
Asn	Leu	Ser	Leu	Pro	Arg	Ser	Thr	Val	Asp	Ser	Leu	Leu	Gln	Xaa	Asn
				165					170						175
Val	Gly	Leu	Gln	Lys	Val	Phe	Leu	Gln	Gly	Tyr	Gln	Leu	His	Leu	Ala
			180					185					190		
Ser	Leu	Cys	Asn	Gly	Ser	Lys	Leu	Glu	Glu	Ile	Ile	Gln	Leu	Gly	Asp
		195					200					205			
Ala	Glu	Val	Ser	Ala	Leu	Cys	Gly	Leu	Pro	Arg	Lys	Lys	Leu	Asp	Ala
	210					215					220				
Ala	Glu	Arg	Val	Leu	Arg	Tyr	Asn	Met	Asp	Ile	Leu	Lys	Pro	Val	Val
	225					230				235					240
Thr	Lys	Leu	Asn	Ser	Thr	Ser	His	Leu	Pro	Thr	Gln	His	Leu	Ala	Glu
			245						250					255	
Ala	Thr	Thr	Val	Leu	Leu	Asp	Ser	Leu	Gly	Gly	Leu	Ala	Gln	Glu	Leu
			260					265					270		
Phe	Ser	Thr	Lys	Ser	Trp	Ser	Asp	Met	Arg	Gln	Glu	Val	Met	Phe	Leu
		275					280					285			
Thr	Asn	Val	Asn	Ser	Ser	Ser	Ser	Ser	Thr	Gln	Ile	Tyr	Gln	Ala	Val
	290						295				300				
Ser	Arg	Ile	Val	Cys	Gly	His	Pro	Glu	Gly	Gly	Gly	Leu	Lys	Ile	Lys
	305				310					315					320
Ser	Leu	Asn	Trp	Tyr	Glu	Asp	Asn	Asn	Tyr	Lys	Ala	Leu	Phe	Gly	Gly
			325						330					335	
Asn	Asn	Thr	Glu	Glu	Asp	Val	Asp	Thr	Phe	Tyr	Asp	Asn	Ser	Thr	Thr
		340						345					350		
Pro	Tyr	Cys	Asn	Asp	Leu	Met	Lys	Asn	Leu	Glu	Ser	Ser	Pro	Leu	Ser
		355					360					365			
Arg	Ile	Ile	Trp	Lys	Ala	Leu	Lys	Pro	Leu	Leu	Val	Gly	Lys	Ile	Leu
	370					375					380				
Tyr	Thr	Pro	Asp	Thr	Pro	Ala	Thr	Arg	Gln	Val	Met	Ala	Glu	Val	Asn
	385				390					395					400
Lys	Thr	Phe	Gln	Glu	Leu	Ala	Val	Phe	His	Asp	Leu	Glu	Gly	Met	Trp
			405						410					415	
Glu	Glu	Leu	Ser	Pro	Gln	Ile	Trp	Thr	Phe	Met	Glu	Asn	Ser	Gln	Glu
			420					425					430		
Met	Asp	Leu	Val	Arg	Thr	Leu	Leu	Asp	Ser	Arg	Gly	Asn	Asp	Gln	Phe
		435					440					445			

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Trp Glu Gln Lys Leu Asp Gly Leu Asp Trp Thr Ala Gln Asp Ile Met
 450 455 460

Ala Phe Leu Ala Lys Asn Pro Glu Asp Val Gln Ser Pro Asn Gly Ser
 465 470 475 480

Val Tyr Thr Trp Arg Glu Ala Phe Asn Glu Thr Asn Gln Ala Ile Gln
 485 490 495

Thr Ile Ser Arg Phe Met Glu Cys Val Asn Leu Asn Lys Leu Glu Pro
 500 505 510

Ile Pro Thr Glu Val Arg Leu Ile Asn Lys Ser Met Glu Leu Leu Asp
 515 520 525

Glu Arg Lys Phe Trp Ala Gly Ile Val Phe Thr Gly Ile Thr Pro Asp
 530 535 540

Ser Val Glu Leu Pro His His Val Lys Tyr Lys Ile Arg Met Asp Ile
 545 550 555 560

Asp Asn Val Glu Arg Thr Asn Lys Ile Lys Asp Gly Tyr Trp Asp Pro
 565 570 575

Gly Pro Arg Ala Asp Pro Phe Glu Asp Met Arg Tyr Val Trp Gly Gly
 580 585 590

Phe Ala Tyr Leu Gln Asp Val Val Glu Gln Ala Ile Ile Arg Val Leu
 595 600 605

Thr Gly Ser Glu Lys Lys Thr Gly Val Tyr Val Gln Gln Met Pro Tyr
 610 615 620

Pro Cys Tyr Val Asp Asp Ile Phe Leu Arg Val Met Ser Arg Ser Met
 625 630 635 640

Pro Leu Phe Met Thr Leu Ala Trp Ile Tyr Ser Val Ala Val Ile Ile
 645 650 655

Lys Ser Ile Val Tyr Glu Lys Glu Ala Arg Leu Lys Glu Thr Met Arg
 660 665 670

Ile Met Gly Leu Asp Asn Gly Ile Leu Trp Phe Ser Trp Phe Val Ser
 675 680 685

Ser Leu Ile Pro Leu Leu Val Ser Ala Gly Leu Leu Val Val Ile Leu
 690 695 700

Lys Leu Gly Asn Leu Leu Pro Tyr Ser Asp Pro Ser Val Val Phe Val
 705 710 715 720

Phe Leu Ser Val Phe Ala Met Val Thr Ile Leu Gln Cys Phe Leu Ile
 725 730 735

Ser Thr Leu Phe Ser Arg Ala Asn Leu Ala Ala Ala Cys Gly Gly Ile
 740 745 750

Ile Tyr Phe Thr Leu Tyr Leu Pro Tyr Val Leu Cys Val Ala Trp Gln
 755 760 765

Asp Tyr Val Gly Phe Ser Ile Lys Ile Phe Ala Ser Leu Leu Ser Pro
 770 775 780

Val Ala Phe Gly Phe Gly Cys Glu Tyr Phe Ala Leu Phe Glu Glu Gln
 785 790 795 800

Gly Ile Gly Val Gln Trp Asp Asn Leu Phe Glu Ser Pro Val Glu Glu
 805 810 815

Asp Gly Phe Asn Leu Thr Thr Ala Val Ser Met Met Leu Phe Asp Thr
 820 825 830

Phe Leu Tyr Gly Val Met Thr Trp Tyr Ile Glu Ala Val Phe Pro Gly
 835 840 845

Gln Tyr Gly Ile Pro Arg Pro Trp Tyr Phe Pro Cys Thr Lys Ser Tyr
 850 855 860

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Trp	Phe	Gly	Glu	Glu	Ile	Asp	Glu	Lys	Ser	His	Pro	Gly	Ser	Ser	Gln	865	870	875	880
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Leu	Gly	Val	Ser	Ile	Gln	Asn	Leu	Val	Lys	Val	Tyr	Arg	Asp	Gly	Met	900	905	910	
Lys	Val	Ala	Val	Asp	Gly	Leu	Ala	Leu	Asn	Phe	Tyr	Glu	Gly	Gln	Ile	915	920	925	
Thr	Ser	Phe	Leu	Gly	His	Asn	Gly	Ala	Gly	Lys	Thr	Thr	Thr	Met	Ser	930	935	940	
Ile	Leu	Thr	Gly	Leu	Phe	Pro	Pro	Thr	Ser	Gly	Thr	Ala	Tyr	Ile	Leu	945	950	955	960
Gly	Lys	Asp	Ile	Arg	Ser	Glu	Met	Ser	Ser	Ile	Arg	Gln	Asn	Leu	Gly	965	970	975	
Val	Cys	Pro	Gln	His	Asn	Val	Leu	Phe	Asp	Met	Leu	Thr	Val	Glu	Glu	980	985	990	
His	Ile	Trp	Phe	Tyr	Ala	Arg	Leu	Lys	Gly	Leu	Ser	Glu	Lys	His	Val	995	1000	1005	
Lys	Ala	Glu	Met	Glu	Gln	Met	Ala	Leu	Asp	Val	Gly	Leu	Pro	Pro	Ser	1010	1015	1020	
Lys	Leu	Lys	Ser	Lys	Thr	Ser	Gln	Leu	Ser	Gly	Gly	Met	Gln	Arg	Lys	1025	1030	1035	1040
Leu	Ser	Val	Ala	Leu	Ala	Phe	Val	Gly	Gly	Ser	Lys	Val	Val	Ile	Leu	1045	1050	1055	
Asp	Glu	Pro	Thr	Ala	Gly	Val	Asp	Pro	Tyr	Ser	Arg	Arg	Gly	Ile	Trp	1060	1065	1070	
Glu	Leu	Leu	Leu	Lys	Tyr	Arg	Gln	Gly	Arg	Thr	Ile	Ile	Leu	Ser	Thr	1075	1080	1085	
His	His	Met	Asp	Glu	Ala	Asp	Ile	Leu	Gly	Asp	Arg	Ile	Ala	Ile	Ile	1090	1095	1100	
Ser	His	Gly	Lys	Leu	Cys	Cys	Val	Gly	Ser	Ser	Leu	Phe	Leu	Lys	Asn	1105	1110	1115	1120
Gln	Leu	Gly	Thr	Gly	Tyr	Tyr	Leu	Thr	Leu	Val	Lys	Lys	Asp	Val	Glu	1125	1130	1135	
Ser	Ser	Leu	Ser	Ser	Cys	Arg	Asn	Ser	Ser	Ser	Thr	Val	Ser	Cys	Leu	1140	1145	1150	
Lys	Lys	Glu	Asp	Ser	Val	Ser	Gln	Ser	Ser	Ser	Asp	Ala	Gly	Leu	Gly	1155	1160	1165	
Ser	Asp	His	Glu	Ser	Asp	Thr	Leu	Thr	Ile	Asp	Val	Ser	Ala	Ile	Ser	1170	1175	1180	
Asn	Leu	Ile	Arg	Lys	His	Val	Ser	Glu	Ala	Arg	Leu	Val	Glu	Asp	Ile	1185	1190	1195	1200
Gly	His	Glu	Leu	Thr	Tyr	Val	Leu	Pro	Tyr	Glu	Ala	Ala	Lys	Glu	Gly	1205	1210	1215	
Ala	Phe	Val	Glu	Leu	Phe	His	Glu	Ile	Asp	Asp	Arg	Leu	Ser	Asp	Leu	1220	1225	1230	
Gly	Ile	Ser	Ser	Tyr	Gly	Ile	Ser	Glu	Thr	Thr	Leu	Glu	Glu	Ile	Phe	1235	1240	1245	
Leu	Lys	Val	Ala	Glu	Glu	Ser	Gly	Val	Asp	Ala	Glu	Thr	Ser	Asp	Gly	1250	1255	1260	
Thr	Leu	Pro	Ala	Arg	Arg	Asn	Arg	Arg	Ala	Phe	Gly	Asp	Lys	Gln	Ser	1265	1270	1275	1280
Cys	Leu	His	Pro	Phe	Thr	Glu	Asp	Asp	Ala	Val	Asp	Pro	Asn	Asp	Ser				

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1285					1290					1295					
Asp	Ile	Asp	Pro	Glu	Ser	Arg	Glu	Thr	Asp	Leu	Leu	Ser	Gly	Met	Asp
			1300					1305					1310		
Gly	Lys	Gly	Ser	Tyr	Gln	Leu	Lys	Gly	Trp	Lys	Leu	Thr	Gln	Gln	Gln
			1315					1320					1325		
Phe	Val	Ala	Leu	Leu	Trp	Lys	Arg	Leu	Leu	Ile	Ala	Arg	Arg	Ser	Arg
			1330					1335					1340		
Lys	Gly	Phe	Phe	Ala	Gln	Ile	Val	Leu	Pro	Ala	Val	Phe	Val	Cys	Ile
								1350					1355		1360
Ala	Leu	Val	Phe	Ser	Leu	Ile	Val	Pro	Pro	Phe	Gly	Lys	Tyr	Pro	Ser
								1370						1375	
Leu	Glu	Leu	Gln	Pro	Trp	Met	Tyr	Asn	Glu	Gln	Tyr	Thr	Phe	Val	Ser
			1380					1385					1390		
Asn	Asp	Ala	Pro	Glu	Asp	Met	Gly	Thr	Gln	Glu	Leu	Leu	Asn	Ala	Leu
			1395					1400					1405		
Thr	Lys	Asp	Pro	Gly	Phe	Gly	Thr	Arg	Cys	Met	Glu	Gly	Asn	Pro	Ile
								1415					1420		
Pro	Asp	Thr	Pro	Cys	Leu	Ala	Gly	Glu	Glu	Asp	Trp	Thr	Ile	Ser	Pro
								1430					1435		1440
Val	Pro	Gln	Ser	Ile	Val	Asp	Leu	Phe	Gln	Asn	Gly	Asn	Trp	Thr	Met
								1445					1450		1455
Lys	Asn	Pro	Ser	Pro	Ala	Cys	Gln	Cys	Ser	Ser	Asp	Lys	Ile	Lys	Lys
								1460					1465		1470
Met	Leu	Pro	Val	Cys	Pro	Pro	Gly	Ala	Gly	Gly	Leu	Pro	Pro	Pro	Gln
								1475					1480		1485
Arg	Lys	Gln	Lys	Thr	Ala	Asp	Ile	Leu	Gln	Asn	Leu	Thr	Gly	Arg	Asn
								1490					1495		1500
Ile	Ser	Asp	Tyr	Leu	Val	Lys	Thr	Tyr	Val	Gln	Ile	Ile	Ala	Lys	Ser
								1505					1510		1515
Leu	Lys	Asn	Lys	Ile	Trp	Val	Asn	Glu	Phe	Arg	Tyr	Gly	Gly	Phe	Ser
								1520					1525		1530
Leu	Gly	Val	Ser	Asn	Ser	Gln	Ala	Leu	Pro	Pro	Ser	His	Glu	Val	Asn
								1535					1540		1545
Asp	Ala	Ile	Lys	Gln	Met	Lys	Lys	Leu	Leu	Lys	Leu	Thr	Lys	Asp	Thr
								1550					1555		1560
Ser	Ala	Asp	Arg	Phe	Leu	Ser	Ser	Leu	Gly	Arg	Phe	Met	Ala	Gly	Leu
								1565					1570		1575
Asp	Thr	Lys	Asn	Asn	Val	Lys	Val	Trp	Phe	Asn	Asn	Lys	Gly	Trp	His
								1580					1585		1590
Ala	Ile	Ser	Ser	Phe	Leu	Asn	Val	Ile	Asn	Asn	Ala	Ile	Leu	Arg	Ala
								1595					1600		1605
Asn	Leu	Gln	Lys	Gly	Glu	Asn	Pro	Ser	Gln	Tyr	Gly	Ile	Thr	Ala	Phe
								1610					1615		1620
Asn	His	Pro	Leu	Asn	Leu	Thr	Lys	Gln	Gln	Leu	Ser	Glu	Val	Ala	Leu
								1625					1630		1635
Met	Thr	Thr	Ser	Val	Asp	Val	Leu	Val	Ser	Ile	Cys	Val	Ile	Phe	Ala
								1640					1645		1650
Met	Ser	Phe	Val	Pro	Ala	Ser	Phe	Val	Val	Phe	Leu	Ile	Gln	Glu	Arg
								1655					1660		1665
Val	Ser	Lys	Ala	Lys	His	Leu	Gln	Phe	Ile	Ser	Gly	Val	Lys	Pro	Val
								1670					1675		1680
Ile	Tyr	Trp	Leu	Ser	Asn	Phe	Val	Trp	Asp	Met	Cys	Asn	Tyr	Val	Val
								1685					1690		1695
								1700					1705		1710

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Pro Ala Thr Leu Val Ile Ile Ile Phe Ile Cys Phe Gln Gln Lys Ser
 1715 1720 1725

Tyr Val Ser Ser Thr Asn Leu Pro Val Leu Ala Leu Leu Leu Leu
 1730 1735 1740

Tyr Gly Trp Ser Ile Thr Pro Leu Met Tyr Pro Ala Ser Phe Val Phe
 1745 1750 1755 1760

Lys Ile Pro Ser Thr Ala Tyr Val Val Leu Thr Ser Val Asn Leu Phe
 1765 1770 1775

Ile Gly Ile Asn Gly Ser Val Ala Thr Phe Val Leu Glu Leu Phe Thr
 1780 1785 1790

Asn Asn Lys Leu Asn Asp Ile Asn Asp Ile Leu Lys Ser Val Phe Leu
 1795 1800 1805

Ile Phe Pro His Phe Cys Leu Gly Arg Gly Leu Ile Asp Met Val Lys
 1810 1815 1820

Asn Gln Ala Met Ala Asp Ala Leu Glu Arg Phe Gly Glu Asn Arg Phe
 1825 1830 1835 1840

Val Ser Pro Leu Ser Trp Asp Leu Val Gly Arg Asn Leu Phe Ala Met
 1845 1850 1855

Ala Val Glu Gly Val Val Phe Phe Leu Ile Thr Val Leu Ile Gln Tyr
 1860 1865 1870

Arg Phe Phe Ile Arg Pro Arg Pro Val Lys Ala Lys Leu Pro Pro Leu
 1875 1880 1885

Asn Asp Glu Asp Glu Asp Val Arg Arg Glu Arg Gln Arg Ile Leu Asp
 1890 1895 1900

Gly Gly Gly Gln Asn Asp Ile Leu Glu Ile Lys Glu Leu Thr Lys Ile
 1905 1910 1915 1920

Tyr Arg Arg Lys Arg Lys Pro Ala Val Asp Arg Ile Cys Ile Gly Ile
 1925 1930 1935

Pro Pro Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys
 1940 1945 1950

Ser Thr Thr Phe Lys Met Leu Thr Gly Asp Thr Pro Val Thr Arg Gly
 1955 1960 1965

Asp Ala Phe Leu Asn Lys Asn Ser Ile Leu Ser Asn Ile His Glu Val
 1970 1975 1980

His Gln Asn Met Gly Tyr Cys Pro Gln Phe Asp Ala Ile Thr Glu Leu
 1985 1990 1995 2000

Leu Thr Gly Arg Glu His Val Glu Phe Phe Ala Leu Leu Arg Gly Val
 2005 2010 2015

Pro Glu Lys Glu Val Gly Lys Phe Gly Glu Trp Ala Ile Arg Lys Leu
 2020 2025 2030

Gly Leu Val Lys Tyr Gly Glu Lys Tyr Ala Ser Asn Tyr Ser Gly Gly
 2035 2040 2045

Asn Lys Arg Lys Leu Ser Thr Ala Met Ala Leu Ile Gly Gly Pro Pro
 2050 2055 2060

Val Val Phe Leu Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg
 2065 2070 2075 2080

Arg Phe Leu Trp Asn Cys Ala Leu Ser Ile Val Lys Glu Gly Arg Ser
 2085 2090 2095

Val Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr
 2100 2105 2110

Arg Met Ala Ile Met Val Asn Gly Arg Phe Arg Cys Leu Gly Ser Val
 2115 2120 2125

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Gln His Leu Lys Asn Arg Phe Gly Asp Gly Tyr Thr Ile Val Val Arg
 2130 2135 2140

Ile Ala Gly Ser Asn Pro Asp Leu Lys Pro Val Gln Glu Phe Phe Gly
 2145 2150 2155 2160

Leu Ala Phe Pro Gly Ser Val Leu Lys Glu Lys His Arg Asn Met Leu
 2165 2170 2175

Gln Tyr Gln Leu Pro Ser Ser Leu Ser Ser Leu Ala Arg Ile Phe Ser
 2180 2185 2190

Ile Leu Ser Gln Ser Lys Lys Arg Leu His Ile Glu Asp Tyr Ser Val
 2195 2200 2205

Ser Gln Thr Thr Leu Asp Gln Val Phe Val Asn Phe Ala Lys Asp Gln
 2210 2215 2220

Ser Asp Asp Asp His Leu Lys Asp Leu Ser Leu His Lys Asn Gln Thr
 2225 2230 2235 2240

Val Val Asp Val Ala Val Leu Thr Ser Phe Leu Gln Asp Glu Lys Val
 2245 2250 2255

Lys Glu Ser Tyr Val
 2260

<210> SEQ ID NO 119
 <211> LENGTH: 1472
 <212> TYPE: PRT
 <213> ORGANISM: Murine sp.
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (250)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (640)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (804)
 <223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 119

Gln Ala Cys Ala Met Glu Ser Arg His Phe Glu Glu Thr Arg Gly Met
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Glu Glu Glu Pro Thr His Leu Pro Leu Val Val Cys Val Asp Lys Leu
 20 25 30

Thr Lys Val Tyr Lys Asn Asp Lys Lys Leu Ala Leu Asn Lys Leu Ser
 35 40 45

Leu Asn Leu Tyr Glu Asn Gln Val Val Ser Phe Leu Gly His Asn Gly
 50 55 60

Ala Gly Lys Thr Thr Thr Met Ser Ile Leu Thr Gly Leu Phe Pro Pro
 65 70 75 80

Thr Ser Gly Ser Ala Thr Ile Tyr Gly His Asp Ile Arg Thr Glu Met
 85 90 95

Asp Glu Ile Arg Lys Asn Leu Gly Met Cys Pro Gln His Asn Val Leu
 100 105 110

Phe Asp Arg Leu Thr Val Glu Glu His Leu Trp Phe Tyr Ser Arg Leu
 115 120 125

Lys Ser Met Ala Gln Glu Glu Ile Arg Lys Glu Thr Asp Lys Met Ile
 130 135 140

Glu Asp Leu Glu Leu Ser Asn Lys Arg His Ser Leu Val Gln Thr Leu
 145 150 155 160

Ser Gly Gly Met Lys Arg Lys Leu Ser Val Ala Ile Ala Phe Val Gly
 165 170 175

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Gly Ser Arg Ala Ile Ile Leu Asp Glu Pro Thr Ala Gly Val Asp Pro
 180 185 190
 Tyr Ala Arg Arg Ala Ile Trp Asp Leu Ile Leu Lys Tyr Lys Pro Gly
 195 200 205
 Arg Thr Ile Leu Leu Ser Thr His His Met Asp Glu Ala Asp Leu Leu
 210 215 220
 Gly Asp Arg Ile Ala Ile Ile Ser His Gly Lys Leu Lys Cys Cys Gly
 225 230 235 240
 Ser Pro Leu Phe Leu Lys Gly Ala Tyr Xaa Asp Gly Tyr Arg Leu Thr
 245 250 255
 Leu Val Lys Gln Pro Ala Glu Pro Gly Thr Ser Gln Glu Pro Gly Leu
 260 265 270
 Ala Ser Ser Pro Ser Gly Cys Pro Arg Leu Ser Ser Cys Ser Glu Pro
 275 280 285
 Gln Val Ser Gln Phe Ile Arg Lys His Val Ala Ser Ser Leu Leu Val
 290 295 300
 Ser Asp Thr Ser Thr Glu Leu Ser Tyr Ile Leu Pro Ser Glu Ala Val
 305 310 315 320
 Lys Lys Gly Ala Phe Glu Arg Leu Phe Gln Gln Leu Glu His Ser Leu
 325 330 335
 Asp Ala Leu His Leu Ser Ser Phe Gly Leu Met Asp Thr Thr Leu Glu
 340 345 350
 Glu Val Phe Leu Lys Val Ser Glu Glu Asp Gln Ser Leu Glu Asn Ser
 355 360 365
 Glu Ala Asp Val Lys Glu Ser Arg Lys Asp Val Leu Pro Gly Ala Glu
 370 375 380
 Gly Leu Thr Ala Val Gly Gly Gln Ala Gly Asn Leu Ala Arg Cys Ser
 385 390 395 400
 Glu Leu Ala Gln Ser Gln Ala Ser Leu Gln Ser Ala Ser Ser Val Gly
 405 410 415
 Ser Ala Arg Gly Glu Glu Gly Thr Gly Tyr Ser Asp Gly Tyr Gly Asp
 420 425 430
 Tyr Arg Pro Leu Phe Asp Asn Leu Gln Asp Pro Asp Asn Val Ser Leu
 435 440 445
 Gln Glu Ala Glu Met Glu Ala Leu Ala Gln Val Gly Gln Gly Ser Arg
 450 455 460
 Lys Leu Glu Gly Trp Trp Leu Lys Met Arg Gln Phe His Gly Leu Leu
 465 470 475 480
 Val Lys Arg Phe His Cys Ala Arg Arg Asn Ser Lys Ala Leu Cys Ser
 485 490 495
 Gln Ile Leu Leu Pro Ala Phe Phe Val Cys Val Ala Met Thr Val Ala
 500 505
 Leu Ser Val Pro Glu Ile Gly Asp Leu Pro Pro Leu Val Leu Ser Pro
 515 520 525
 Ser Gln Tyr His Asn Tyr Thr Gln Pro Arg Gly Asn Phe Ile Pro Tyr
 530 535 540
 Ala Asn Glu Glu Arg Gln Glu Tyr Arg Leu Arg Leu Ser Pro Asp Ala
 545 550 555 560
 Ser Pro Gln Gln Leu Val Ser Thr Phe Arg Leu Pro Ser Gly Val Gly
 565 570 575
 Ala Thr Cys Val Leu Lys Ser Pro Ala Asn Gly Ser Leu Gly Pro Met
 580 585 590

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Leu	Asn	Leu	Ser	Ser	Gly	Glu	Ser	Arg	Leu	Leu	Ala	Ala	Arg	Phe	Phe
		595					600					605			
Asp	Ser	Met	Cys	Leu	Glu	Ser	Phe	Thr	Gln	Gly	Leu	Pro	Leu	Ser	Asn
	610				615					620					
Phe	Val	Pro	Pro	Pro	Pro	Ser	Pro	Ala	Pro	Ser	Asp	Ser	Pro	Val	Xaa
625					630					635					640
Pro	Asp	Glu	Asp	Ser	Leu	Gln	Ala	Trp	Asn	Met	Ser	Leu	Pro	Pro	Thr
				645					650					655	
Ala	Gly	Pro	Glu	Thr	Trp	Thr	Ser	Ala	Pro	Ser	Leu	Pro	Arg	Leu	Val
			660					665					670		
His	Glu	Pro	Val	Arg	Cys	Thr	Cys	Ser	Ala	Gln	Gly	Thr	Gly	Phe	Ser
		675					680					685			
Cys	Pro	Ser	Ser	Val	Gly	Gly	His	Pro	Pro	Gln	Met	Arg	Val	Val	Thr
	690					695					700				
Gly	Asp	Ile	Leu	Thr	Asp	Ile	Thr	Gly	His	Asn	Val	Ser	Glu	Tyr	Leu
705					710					715					720
Leu	Phe	Thr	Ser	Asp	Arg	Phe	Arg	Leu	His	Arg	Tyr	Gly	Ala	Ile	Thr
				725					730					735	
Phe	Gly	Asn	Val	Gln	Lys	Ser	Ile	Pro	Ala	Ser	Phe	Gly	Ala	Arg	Val
			740					745					750		
Pro	Pro	Met	Val	Arg	Lys	Ile	Ala	Val	Arg	Arg	Val	Ala	Gln	Val	Leu
		755					760					765			
Tyr	Asn	Asn	Lys	Gly	Tyr	His	Ser	Met	Pro	Thr	Tyr	Leu	Asn	Ser	Leu
	770					775					780				
Asn	Asn	Ala	Ile	Leu	Arg	Ala	Asn	Leu	Pro	Lys	Ser	Lys	Gly	Asn	Pro
785					790					795					800
Ala	Ala	Tyr	Xaa	Ile	Thr	Val	Thr	Asn	His	Pro	Met	Asn	Lys	Thr	Ser
				805					810					815	
Ala	Ser	Leu	Ser	Leu	Asp	Tyr	Leu	Leu	Gln	Gly	Thr	Asp	Val	Val	Ile
			820					825					830		
Ala	Ile	Phe	Ile	Ile	Val	Ala	Met	Ser	Phe	Val	Pro	Ala	Ser	Phe	Val
		835					840					845			
Val	Phe	Leu	Val	Ala	Glu	Lys	Ser	Thr	Lys	Ala	Lys	His	Leu	Gln	Phe
	850					855					860				
Val	Ser	Gly	Cys	Asn	Pro	Val	Ile	Tyr	Trp	Leu	Ala	Asn	Tyr	Val	Trp
865					870					875					880
Asp	Met	Leu	Asn	Tyr	Leu	Val	Pro	Ala	Thr	Cys	Cys	Val	Ile	Ile	Leu
				885					890					895	
Phe	Val	Phe	Asp	Leu	Pro	Ala	Tyr	Thr	Ser	Pro	Thr	Asn	Phe	Pro	Ala
			900					905					910		
Val	Leu	Ser	Leu	Phe	Leu	Leu	Tyr	Gly	Trp	Ser	Ile	Thr	Pro	Ile	Met
			915				920					925			
Tyr	Pro	Ala	Ser	Phe	Trp	Phe	Glu	Val	Pro	Ser	Ser	Ala	Tyr	Val	Phe
						935					940				
Leu	Ile	Val	Ile	Asn	Leu	Phe	Ile	Gly	Ile	Thr	Ala	Thr	Val	Ala	Thr
945					950					955					960
Phe	Leu	Leu	Gln	Leu	Phe	Glu	His	Asp	Lys	Asp	Leu	Lys	Val	Val	Asn
				965					970					975	
Ser	Tyr	Leu	Lys	Ser	Cys	Phe	Leu	Ile	Phe	Pro	Asn	Tyr	Asn	Leu	Gly
			980					985					990		
His	Gly	Leu	Met	Glu	Met	Ala	Tyr	Asn	Glu	Tyr	Ile	Asn	Glu	Tyr	Tyr
							1000						1005		
Ala	Lys	Ile	Gly	Gln	Phe	Asp	Lys	Met	Lys	Ser	Pro	Phe	Glu	Trp	Asp

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1010	1015	1020
Ile Val Thr Arg Gly Leu Val Ala Met Thr Val Glu Gly Phe Val Gly 1025	1030	1035 1040
Phe Phe Leu Thr Ile Met Cys Gln Tyr Asn Phe Leu Arg Gln Pro Gln 1045	1050	1055
Arg Leu Pro Val Ser Thr Lys Pro Val Glu Asp Asp Val Asp Val Ala 1060	1065	1070
Ser Glu Arg Gln Arg Val Leu Arg Gly Asp Ala Asp Asn Asp Met Val 1075	1080	1085
Lys Ile Glu Asn Leu Thr Lys Val Tyr Lys Ser Arg Lys Ile Gly Arg 1090	1095	1100
Ile Leu Ala Val Asp Arg Leu Cys Leu Gly Val Cys Val Pro Gly Glu 1105	1110	1115 1120
Cys Phe Gly Leu Leu Gly Val Asn Gly Ala Gly Lys Thr Ser Thr Phe 1125	1130	1135
Lys Met Leu Thr Gly Asp Glu Ser Thr Thr Gly Gly Glu Ala Phe Val 1140	1145	1150
Asn Gly His Ser Val Leu Lys Asp Leu Leu Gln Val Gln Gln Ser Leu 1155	1160	1165
Gly Tyr Cys Pro Gln Phe Asp Val Pro Val Asp Glu Leu Thr Ala Arg 1170	1175	1180
Glu His Leu Gln Leu Tyr Thr Arg Leu Arg Cys Ile Pro Trp Lys Asp 1185	1190	1195 1200
Glu Ala Gln Val Val Lys Trp Ala Leu Glu Lys Leu Glu Leu Thr Lys 1205	1210	1215
Tyr Ala Asp Lys Pro Ala Gly Thr Tyr Ser Gly Gly Asn Lys Arg Lys 1220	1225	1230
Leu Ser Thr Ala Ile Ala Leu Ile Gly Tyr Pro Ala Phe Ile Phe Leu 1235	1240	1245
Asp Glu Pro Thr Thr Gly Met Asp Pro Lys Ala Arg Arg Phe Leu Trp 1250	1255	1260
Asn Leu Ile Leu Asp Leu Ile Lys Thr Gly Arg Ser Val Val Leu Thr 1265	1270	1275 1280
Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys Thr Arg Leu Ala Ile 1285	1290	1295
Met Val Asn Gly Arg Leu His Cys Leu Gly Ser Ile Gln His Leu Lys 1300	1305	1310
Asn Arg Phe Gly Asp Gly Tyr Met Ile Thr Val Arg Thr Lys Ser Ser 1315	1320	1325
Gln Asn Val Lys Asp Val Val Arg Phe Phe Asn Arg Asn Phe Pro Glu 1330	1335	1340
Ala His Ala Gln Gly Lys Thr Pro Tyr Lys Val Gln Tyr Gln Leu Lys 1345	1350	1355 1360
Ser Glu His Ile Ser Leu Ala Gln Val Phe Ser Lys Met Glu Gln Val 1365	1370	1375
Val Gly Val Leu Gly Ile Glu Asp Tyr Ser Val Ser Gln Thr Thr Leu 1380	1385	1390
Asp Asn Val Phe Val Asn Phe Ala Lys Lys Gln Ser Asp Asn Val Glu 1395	1400	1405
Gln Gln Glu Ala Glu Pro Ser Ser Leu Pro Ser Pro Leu Gly Leu Leu 1410	1415	1420
Ser Leu Leu Arg Pro Arg Pro Ala Pro Thr Glu Leu Arg Ala Leu Val 1425	1430	1435 1440

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Ala Asp Glu Pro Glu Asp Leu Asp Thr Glu Asp Glu Gly Leu Ile Ser
 1445 1450 1455

Phe Glu Glu Glu Arg Ala Gln Leu Ser Phe Asn Thr Asp Thr Leu Cys
 1460 1465 1470

<210> SEQ ID NO 120

<211> LENGTH: 1704

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Met Ala Val Leu Arg Gln Leu Ala Leu Leu Leu Trp Lys Asn Tyr Thr
 1 5 10 15

Leu Gln Lys Arg Lys Val Leu Val Thr Val Leu Glu Leu Phe Leu Pro
 20 25 30

Leu Leu Phe Ser Gly Ile Leu Ile Trp Leu Arg Leu Lys Ile Gln Ser
 35 40 45

Glu Asn Val Pro Asn Ala Thr Ile Tyr Pro Gly Gln Ser Ile Gln Glu
 50 55 60

Leu Pro Leu Phe Phe Thr Phe Pro Pro Pro Gly Asp Thr Trp Glu Leu
 65 70 75 80

Ala Tyr Ile Pro Ser His Ser Asp Ala Ala Lys Thr Val Thr Glu Thr
 85 90 95

Val Arg Arg Ala Leu Val Ile Asn Met Arg Val Arg Gly Phe Pro Ser
 100 105 110

Glu Lys Asp Phe Glu Asp Tyr Ile Arg Tyr Asp Asn Cys Ser Ser Ser
 115 120 125

Val Leu Ala Ala Val Val Phe Glu His Pro Phe Asn His Ser Lys Glu
 130 135 140

Pro Leu Pro Leu Ala Val Lys Tyr His Leu Arg Phe Ser Tyr Thr Arg
 145 150 155 160

Arg Asn Tyr Met Trp Thr Gln Thr Gly Ser Phe Phe Leu Lys Glu Thr
 165 170 175

Glu Gly Trp His Thr Thr Ser Leu Phe Pro Leu Phe Pro Asn Pro Gly
 180 185 190

Pro Arg Glu Pro Thr Ser Pro Asp Gly Gly Glu Pro Gly Tyr Ile Arg
 195 200 205

Glu Gly Phe Leu Ala Val Gln His Ala Val Asp Arg Ala Ile Met Glu
 210 215 220

Tyr His Ala Asp Ala Ala Thr Arg Gln Leu Phe Gln Arg Leu Thr Val
 225 230 235 240

Thr Ile Lys Arg Phe Pro Tyr Pro Pro Phe Ile Ala Asp Pro Phe Leu
 245 250 255

Val Ala Ile Gln Tyr Gln Leu Pro Leu Leu Leu Leu Leu Ser Phe Thr
 260 265 270

Tyr Thr Ala Leu Thr Ile Ala Arg Ala Val Val Gln Glu Lys Glu Arg
 275 280 285

Arg Leu Lys Glu Tyr Met Arg Met Met Gly Leu Ser Ser Trp Leu His
 290 295 300

Trp Ser Ala Trp Phe Leu Leu Phe Phe Leu Phe Leu Leu Ile Ala Ala
 305 310 315 320

Ser Phe Met Thr Leu Leu Phe Cys Val Lys Val Lys Pro Asn Val Ala
 325 330 335

Val Leu Ser Arg Ser Asp Pro Ser Leu Val Leu Ala Phe Leu Leu Cys

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340					345					350					
Phe	Ala	Ile	Ser	Thr	Ile	Ser	Phe	Ser	Phe	Met	Val	Ser	Thr	Phe	Phe
	355						360					365			
Ser	Lys	Ala	Asn	Met	Ala	Ala	Ala	Phe	Gly	Gly	Phe	Leu	Tyr	Phe	Phe
	370					375					380				
Thr	Tyr	Ile	Pro	Tyr	Phe	Phe	Val	Ala	Pro	Arg	Tyr	Asn	Trp	Met	Thr
385					390					395					400
Leu	Ser	Gln	Lys	Leu	Cys	Ser	Cys	Leu	Leu	Ser	Asn	Val	Ala	Met	Ala
				405					410					415	
Met	Gly	Ala	Gln	Leu	Ile	Gly	Lys	Phe	Glu	Ala	Lys	Gly	Met	Gly	Ile
			420					425					430		
Gln	Trp	Arg	Asp	Leu	Leu	Ser	Pro	Val	Asn	Val	Asp	Asp	Asp	Phe	Cys
		435					440					445			
Phe	Gly	Gln	Val	Leu	Gly	Met	Leu	Leu	Leu	Asp	Ser	Val	Leu	Tyr	Gly
	450					455						460			
Leu	Val	Thr	Trp	Tyr	Met	Glu	Ala	Val	Phe	Pro	Gly	Gln	Phe	Gly	Val
465					470					475					480
Pro	Gln	Pro	Trp	Tyr	Phe	Phe	Ile	Met	Pro	Ser	Tyr	Trp	Cys	Gly	Lys
				485					490					495	
Pro	Arg	Ala	Val	Ala	Gly	Lys	Glu	Glu	Glu	Asp	Ser	Asp	Pro	Glu	Lys
			500					505					510		
Ala	Leu	Arg	Asn	Glu	Tyr	Phe	Glu	Ala	Glu	Pro	Glu	Asp	Leu	Val	Ala
		515					520					525			
Gly	Ile	Lys	Ile	Lys	His	Leu	Ser	Lys	Val	Phe	Arg	Val	Gly	Asn	Lys
	530					535					540				
Asp	Arg	Ala	Ala	Val	Arg	Asp	Leu	Asn	Leu	Asn	Leu	Tyr	Glu	Gly	Gln
545					550					555					560
Ile	Thr	Val	Leu	Leu	Gly	His	Asn	Gly	Ala	Gly	Lys	Thr	Thr	Thr	Leu
				565					570						575
Ser	Met	Leu	Thr	Gly	Leu	Phe	Pro	Pro	Thr	Ser	Gly	Arg	Ala	Tyr	Ile
			580					585					590		
Ser	Gly	Tyr	Glu	Ile	Ser	Gln	Asp	Met	Val	Gln	Ile	Arg	Lys	Ser	Leu
		595					600					605			
Gly	Leu	Cys	Pro	Gln	His	Asp	Ile	Leu	Phe	Asp	Asn	Leu	Thr	Val	Ala
	610					615					620				
Glu	His	Leu	Tyr	Phe	Tyr	Ala	Gln	Leu	Lys	Gly	Leu	Ser	Arg	Gln	Lys
625					630					635					640
Cys	Pro	Glu	Glu	Val	Lys	Gln	Met	Leu	His	Ile	Ile	Gly	Leu	Glu	Asp
				645					650					655	
Lys	Trp	Asn	Ser	Arg	Ser	Arg	Phe	Leu	Ser	Gly	Gly	Met	Arg	Arg	Lys
			660					665					670		
Leu	Ser	Ile	Gly	Ile	Ala	Leu	Ile	Ala	Gly	Ser	Lys	Val	Leu	Ile	Leu
		675					680					685			
Asp	Glu	Pro	Thr	Ser	Gly	Met	Asp	Ala	Ile	Ser	Arg	Arg	Ala	Ile	Trp
	690					695					700				
Asp	Leu	Leu	Gln	Arg	Gln	Lys	Ser	Asp	Arg	Thr	Ile	Val	Leu	Thr	Thr
705					710					715					720
His	Phe	Met	Asp	Glu	Ala	Asp	Leu	Leu	Gly	Asp	Arg	Ile	Ala	Ile	Met
				725					730					735	
Ala	Lys	Gly	Glu	Leu	Gln	Cys	Cys	Gly	Ser	Ser	Leu	Phe	Leu	Lys	Gln
			740					745					750		
Lys	Tyr	Gly	Ala	Gly	Tyr	His	Met	Thr	Leu	Val	Lys	Glu	Pro	His	Cys
		755					760					765			

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Asn	Pro	Glu	Asp	Ile	Ser	Gln	Leu	Val	His	His	His	Val	Pro	Asn	Ala
	770					775					780				
Thr	Leu	Glu	Ser	Ser	Ala	Gly	Ala	Glu	Leu	Ser	Phe	Ile	Leu	Pro	Arg
785					790					795					800
Glu	Ser	Thr	His	Arg	Phe	Glu	Gly	Leu	Phe	Ala	Lys	Leu	Glu	Lys	Lys
				805					810					815	
Gln	Lys	Glu	Leu	Gly	Ile	Ala	Ser	Phe	Gly	Ala	Ser	Ile	Thr	Thr	Met
			820					825					830		
Glu	Glu	Val	Phe	Leu	Arg	Val	Gly	Lys	Leu	Val	Asp	Ser	Ser	Met	Asp
		835					840				845				
Ile	Gln	Ala	Ile	Gln	Leu	Pro	Ala	Leu	Gln	Tyr	Gln	His	Glu	Arg	Arg
	850					855					860				
Ala	Ser	Asp	Trp	Ala	Val	Asp	Ser	Asn	Leu	Cys	Gly	Ala	Met	Asp	Pro
865					870					875					880
Ser	Asp	Gly	Ile	Gly	Ala	Leu	Ile	Glu	Glu	Glu	Arg	Thr	Ala	Val	Lys
				885					890					895	
Leu	Asn	Thr	Gly	Leu	Ala	Leu	His	Cys	Gln	Gln	Phe	Trp	Ala	Met	Phe
			900					905					910		
Leu	Lys	Lys	Ala	Ala	Tyr	Ser	Trp	Arg	Glu	Trp	Lys	Met	Val	Ala	Ala
		915					920					925			
Gln	Val	Leu	Val	Pro	Leu	Thr	Cys	Val	Thr	Leu	Ala	Leu	Leu	Ala	Ile
	930					935					940				
Asn	Tyr	Ser	Ser	Glu	Leu	Phe	Asp	Asp	Pro	Met	Leu	Arg	Leu	Thr	Leu
945					950					955					960
Gly	Glu	Tyr	Gly	Arg	Thr	Val	Val	Pro	Phe	Ser	Val	Pro	Gly	Thr	Ser
				965					970					975	
Gln	Leu	Gly	Gln	Gln	Leu	Ser	Glu	His	Leu	Lys	Asp	Ala	Leu	Gln	Ala
			980					985					990		
Glu	Gly	Gln	Glu	Pro	Arg	Glu	Val	Leu	Gly	Asp	Leu	Glu	Glu	Phe	Leu
		995					1000					1005			
Ile	Phe	Arg	Ala	Ser	Val	Glu	Gly	Gly	Gly	Phe	Asn	Glu	Arg	Cys	Leu
	1010					1015					1020				
Val	Ala	Ala	Ser	Phe	Arg	Asp	Val	Gly	Glu	Arg	Thr	Val	Val	Asn	Ala
1025					1030					1035					1040
Leu	Phe	Asn	Asn	Gln	Ala	Tyr	His	Ser	Pro	Ala	Thr	Ala	Leu	Ala	Val
				1045					1050					1055	
Val	Asp	Asn	Leu	Leu	Phe	Lys	Leu	Leu	Cys	Gly	Pro	His	Ala	Ser	Ile
		1060						1065					1070		
Val	Val	Ser	Asn	Phe	Pro	Gln	Pro	Arg	Ser	Ala	Leu	Gln	Ala	Ala	Lys
		1075					1080					1085			
Asp	Gln	Phe	Asn	Glu	Gly	Arg	Lys	Gly	Phe	Asp	Ile	Ala	Leu	Asn	Leu
1090						1095					1100				
Leu	Phe	Ala	Met	Ala	Phe	Leu	Ala	Ser	Thr	Phe	Ser	Ile	Leu	Ala	Val
1105					1110					1115					1120
Ser	Glu	Arg	Ala	Val	Gln	Ala	Lys	His	Val	Gln	Phe	Val	Ser	Gly	Val
				1125					1130					1135	
His	Val	Ala	Ser	Phe	Trp	Leu	Ser	Ala	Leu	Leu	Trp	Asp	Leu	Ile	Ser
		1140						1145					1150		
Phe	Leu	Ile	Pro	Ser	Leu	Leu	Leu	Leu	Val	Val	Phe	Lys	Ala	Phe	Asp
	1155						1160					1165			
Val	Arg	Ala	Phe	Thr	Arg	Asp	Gly	His	Met	Ala	Asp	Thr	Leu	Leu	Leu
	1170					1175					1180				

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Leu	Leu	Leu	Tyr	Gly	Trp	Ala	Ile	Ile	Pro	Leu	Met	Tyr	Leu	Met	Asn
1185					1190					1195					1200
Phe	Phe	Phe	Leu	Gly	Ala	Ala	Thr	Ala	Tyr	Thr	Arg	Leu	Thr	Ile	Phe
				1205					1210					1215	
Asn	Ile	Leu	Ser	Gly	Ile	Ala	Thr	Phe	Leu	Met	Val	Thr	Ile	Met	Arg
			1220					1225						1230	
Ile	Pro	Ala	Val	Lys	Leu	Glu	Glu	Leu	Ser	Lys	Thr	Leu	Asp	His	Val
		1235						1240					1245		
Phe	Leu	Val	Leu	Pro	Asn	His	Cys	Leu	Gly	Met	Ala	Val	Ser	Ser	Phe
	1250					1255					1260				
Tyr	Glu	Asn	Tyr	Glu	Thr	Arg	Arg	Tyr	Cys	Thr	Ser	Ser	Glu	Val	Ala
1265					1270					1275					1280
Ala	His	Tyr	Cys	Lys	Lys	Tyr	Asn	Ile	Gln	Tyr	Gln	Glu	Asn	Phe	Tyr
				1285					1290						1295
Ala	Trp	Ser	Ala	Pro	Gly	Val	Gly	Arg	Phe	Val	Ala	Ser	Met	Ala	Ala
			1300					1305						1310	
Ser	Gly	Cys	Ala	Tyr	Leu	Ile	Leu	Leu	Phe	Leu	Ile	Glu	Thr	Asn	Leu
		1315					1320						1325		
Leu	Gln	Arg	Leu	Arg	Gly	Ile	Leu	Cys	Ala	Leu	Arg	Arg	Arg	Arg	Thr
	1330					1335					1340				
Leu	Thr	Glu	Leu	Tyr	Thr	Arg	Met	Pro	Val	Leu	Pro	Glu	Asp	Gln	Asp
1345					1350						1355				1360
Val	Ala	Asp	Glu	Arg	Thr	Arg	Ile	Leu	Ala	Pro	Ser	Pro	Asp	Ser	Leu
				1365					1370						1375
Leu	His	Thr	Pro	Leu	Ile	Ile	Lys	Glu	Leu	Ser	Lys	Val	Tyr	Glu	Gln
			1380					1385						1390	
Arg	Val	Pro	Leu	Leu	Ala	Val	Asp	Arg	Leu	Ser	Leu	Ala	Val	Gln	Lys
		1395					1400						1405		
Gly	Glu	Cys	Phe	Gly	Leu	Leu	Gly	Phe	Asn	Gly	Ala	Gly	Lys	Thr	Thr
	1410					1415					1420				
Thr	Phe	Lys	Met	Leu	Thr	Gly	Glu	Glu	Ser	Leu	Thr	Ser	Gly	Asp	Ala
1425					1430					1435					1440
Phe	Val	Gly	Gly	His	Arg	Ile	Ser	Ser	Asp	Val	Gly	Lys	Val	Arg	Gln
				1445					1450						1455
Arg	Ile	Gly	Tyr	Cys	Pro	Gln	Phe	Asp	Ala	Leu	Leu	Asp	His	Met	Thr
			1460					1465						1470	
Gly	Arg	Glu	Met	Leu	Val	Met	Tyr	Ala	Arg	Leu	Arg	Gly	Ile	Pro	Glu
		1475					1480						1485		
Arg	His	Ile	Gly	Ala	Cys	Val	Glu	Asn	Thr	Leu	Arg	Gly	Leu	Leu	Leu
	1490						1495					1500			
Glu	Pro	His	Ala	Asn	Lys	Leu	Val	Arg	Thr	Tyr	Ser	Gly	Gly	Asn	Lys
1505					1510						1515				1520
Arg	Lys	Leu	Ser	Thr	Gly	Ile	Ala	Leu	Ile	Gly	Glu	Pro	Ala	Val	Ile
				1525						1530					1535
Phe	Leu	Asp	Glu	Pro	Ser	Thr	Gly	Met	Asp	Pro	Val	Ala	Arg	Arg	Leu
			1540					1545						1550	
Leu	Trp	Asp	Thr	Val	Ala	Arg	Ala	Arg	Glu	Ser	Gly	Lys	Ala	Ile	Ile
		1555					1560						1565		
Ile	Thr	Ser	His	Ser	Met	Glu	Glu	Cys	Glu	Ala	Leu	Cys	Thr	Arg	Leu
	1570						1575					1580			
Ala	Ile	Met	Val	Gln	Gly	Gln	Phe	Lys	Cys	Leu	Gly	Ser	Pro	Gln	His
1585					1590					1595					1600
Leu	Lys	Ser	Lys	Phe	Gly	Ser	Gly	Tyr	Ser	Leu	Arg	Ala	Lys	Val	Gln

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1605	1610	1615
Ser Glu Gly Gln Gln Glu Ala Leu Glu Glu Phe Lys Ala Phe Val Asp		
1620	1625	1630
Leu Thr Phe Pro Gly Ser Val Leu Glu Asp Glu His Gln Gly Met Val		
1635	1640	1645
His Tyr His Leu Pro Gly Arg Asp Leu Ser Trp Ala Lys Val Phe Gly		
1650	1655	1660
Ile Leu Glu Lys Ala Lys Glu Lys Tyr Gly Val Asp Asp Tyr Ser Val		
1665	1670	1675
Ser Gln Ile Ser Leu Glu Gln Val Phe Leu Ser Phe Ala His Leu Gln		
1685	1690	1695
Pro Pro Thr Ala Glu Glu Gly Arg		
1700		

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What is claimed is:

1. A purified nucleic acid molecule comprising a nucleic acid sequence encoding a retina-specific ATP-binding cassette transporter comprising the amino acid sequence of SEQ ID NO:3 except wherein said amino acid sequence comprises the mutation.
2. An expression vector comprising the nucleic acid molecule of claim 1.

3. An isolated host cell comprising the expression vector of claim 2.
4. A cell culture comprising at least one cell comprising the expression vector of claim 2.
5. A composition comprising an effective amount of the nucleic acid molecule of claim 1 and a pharmaceutically acceptable carrier.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,141,420 B2
APPLICATION NO. : 10/340097
DATED : November 28, 2006
INVENTOR(S) : Rando Allikmets et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page,

Item (56), **References Cited:**

OTHER PUBLICATIONS

Page 2, "Allikmets, R., et al.," reference, delete "eukaryotic" and insert -- eukaryotic --

Page 2, "Cline, M.J.," reference, delete "69-62," and insert -- 69-92. --.

Page 3, "Stone, E.M., et al.," reference, delete "Stagardt-Like" and insert -- Stargardt-Like --.

Page 3, "Gerber, S., et al.," reference, delete "Statrgardt" and insert -- Stargardt --.

Column 10,

Line 6, delete "ANABCR" and insert -- An ABCR --.

Column 16,

Line 18, delete "maybe" and insert -- may be --.

Line 21, after "may" delete "be",

Line 47, delete "³²p," and insert -- ³²P, --.

Column 21,

Line 57, delete "that^a" and insert -- that ^a --.

Column 22,

Line 12, delete "Hofinann," and insert -- Hofmann, --.

Line 16, delete "CDNA" and insert -- cDNA --.

Column 23,

Line 1, delete "(Glavč" and insert -- (Glavač --.

Column 27,

Lines 13-14, delete "imrnmunocytochemistry" and insert -- immunocytochemistry --.

Line 14, delete "findus" and insert -- fundus --.

Column 28,

Line 8, delete "aclinical" and insert -- a clinical --.

Column 29,

Line 18, delete "Domer," and insert -- Domer, --.

Line 28, delete "RCC1" and insert -- RCC1 --.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,141,420 B2
APPLICATION NO. : 10/340097
DATED : November 28, 2006
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Page 2 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 30,

Line 39, delete "Bems," and insert -- Berns, --.

Line 41, delete "mdr2" and insert -- mdr2--.

Column 133,

Line 26, delete "mutation." and insert -- mutation A1028V. --.

Signed and Sealed this

Twentieth Day of November, 2007

A handwritten signature in black ink on a dotted background. The signature reads "Jon W. Dudas" in a cursive style.

JON W. DUDAS

Director of the United States Patent and Trademark Office